TCu380A Intrauterine Contraceptive Device (IUD)

WHO/UNFPA Technical Specification and Prequalification Guidance

2016
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TCu380A Intrauterine Contraceptive Device (IUD)


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TCu380A Intrauterine Contraceptive Device (IUD)

Keywords
Contraceptive medical devices, TCu380A IUD, Intrauterine devices, copper,
Contraception - instrumentation, WHO/UNFPA prequalification programme,
Application for prequalification, Prequalification inspection, Prequalification guidance,
Technical specification, Quality assurance, Quality control, FHI360,
United Nations Population Fund (UNFPA), U.S. Agency for International Development (USAID),
World Health Organization

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This document is a result of a review of the latest available evidence and an extensive consultative consensus-building process with individuals who represent the TCu380A Intrauterine Contraceptive Device (IUD) manufacturing industry, the International Organization for Standardization (ISO), testing laboratories, national regulatory authorities, research institutes, bulk procurement agencies, social marketing companies, international agencies, nongovernmental organizations, consumer groups, and family planning policy-makers and programme managers.

The World Health Organization, Department of Reproductive Health and Research (WHO/RHR), the United Nations Population Fund (UNFPA), the United States Agency for International Development (USAID), the Bill and Melinda Gates Foundation and FHI 360 (former Family Health International) all have supported publication of this document and would like to gratefully acknowledge the contributions of the following people and organizations:

Co-authors
William Potter, Stapleford Scientific Services Ltd, and Paul Hayes, Kingsway Management Services Ltd., led the development of this document in close collaboration with Annika Schwenk, UNFPA, and Hayley Traeger, UNFPA.

IUD Technical Review Committee and external reviewers
The co-authors worked closely with other committee members and external reviewers who, in addition to attending the IUD Technical Review Committee Meeting, have on their own time participated in ongoing electronic discussions and the extensive review process. Committee members include Morten Sorensen, UNFPA; Lisa Hedman, WHO/DEM; Mario Philip R. Festin, WHO/RHR; Frederik Kristensen, WHO; Viviana Mangiaterra, WHO/RHR; Elena Uderzo, WHO/RHR; Margaret Usher-Patel, WHO/RHR; Adriana Velazquez Berumen, WHO/DEM; Paul O’Brien, Westside Contraceptive Services; K. Sivakumar, Pharmedics Technical Services Prv. Ltd.; Nuriye Ortayli, UNFPA; Vinit Sharma, UNFPA; John Geroft, Enersol Pty. Ltd; Luis Lleras, FHI360; Allen All, FHI360; Steve Hamel, FHI360; Jeffery Tremelling, FHI360; Patrick Hoet, ADEES; Jakub Srebro, JSIAI; Nils Ekeroth, ekeroth Quality AB - eQ AB; Carolina Martignoni, QUARA GROUP.

External reviewers and participants of the 2014 review meeting in India include Basab Mukherjee, FOGS1; Sharad Agarwal, HLFPP-T-Noida; Nadeem Akhtar Khan, HLFPP-T-Noida; Rashmi Asif, Jhpiegio; Avina Sarna, Population Council; Regine Sitrak-Ware, MD Population Council; Avina Sarna, Population Council; Sharad Singh, PSI; Sharad Singh, PSI India; K. Bharathidasan, SGS India Private Limited, Chennai; K. Bharathidasan, SGS India Private Limited, Chennai; Raghvendra Sharma, SGS-Life Science services; Anchita Patil, UNFPA.

IUD manufacturers
We greatly acknowledge the support that manufacturers have given to this review process. Munni Maurya, Contech Devices Pvt Ltd/Noida, India; Praveen Shukla, Contech Devices Pvt Ltd/Noida, India; Abhishek Yadav, Contech Devices Pvt Ltd/Noida, India; Vinod Kumat, Corporate Channels India Pvt. Ltd. Udaipur; Ramnick Kumar Dagria, Corporate Channels India Pvt. Ltd., Udaipur; Manoj Bhalkikar, Famy Care Limited, India; Pradip Shah, Famy Care Limited, India; Premasagar B, HLL Lifecare Limited, Thiruvananthapuram, India; Mukund.R, HLL Lifecare Limited, Thiruvananthapuram, India; Jitesh Prabhu S L, HLL Lifecare Limited/Kochi, Kerala, India; Renata Canteiro, Injeflex, Brazil; Ratnesh Lal, Mercck for Mothers/MSD Pvt. Ltd. India; Srinivasa Pardhasaradhi, MSD Ltd. India; Ajit Raje, Regina International Ltd. India; Sanjay Temgire, Regina International Ltd. India; Vivek Kudalkar, SMB Corporation of India; Anupam Rai, SMB Corporation of India; Girish R. Shah, SMB Corporation of India.
**Acknowledgements**

**WHO and UNFPA support**

The success of the Technical Committees and the workshops held by WHO and UNFPA would not have been possible except for the very efficient support provided by Mario Philip R. Festin, WHO/RHR; Morten Sorensen, UNFPA and Hayley Traeger, UNFPA.
Introduction

This document, the revised World Health Organization (WHO)/United Nations Population Fund (UNFPA) TCu380A Intrauterine Contraceptive Device (IUD) Technical Specification and Prequalification Guidance 2016, is designed to provide manufacturers, procurement agencies, national regulatory authorities, testing laboratories and programme managers with up-to-date information about the TCu380A IUD. It includes a comprehensive introduction to WHO/UNFPA Prequalification Programme for the TCu380A IUDs, explains essential elements of IUD quality assurance and provides the detailed TCu380A IUD Technical Specification in Chapter 3. The document in hand gives guidance for bioburden control and terminal sterilisation as well as on stability studies.

The Technical Basis Paper in Annex I is to be used as background information and reference paper. It includes a description of the historical process for the development of TCu380A specifications and justification for the changes that have been made against the 2010 guidelines.

In Annex II, summary for changes to the specification are listed in table format. Further Annexes provide technical drawings and list product dossier and site master file requirements. The guide for prequalification inspections, Annex V, is a well-established tool for inspectors and manufacturers.

Background

Globally, intrauterine devices (IUDs) are cited as the second most widely used contraceptive method. Copper-bearing IUDs come in a variety of designs. The IUD recommended by WHO for bulk procurement is the TCu380A. The frame of the TCu380A IUD is “T”-shaped. The horizontal arms of the “T” keep the IUD in place within the uterus. Copper-bearing IUDs usually consist of a plastic body to which copper is attached. In the earlier models the copper was wound around the vertical stem only, but in more recent designs copper sleeves have been added to the horizontal arms to increase the surface area of copper and thus improve efficacy.

In 2006 a Cochrane Review of copper-bearing IUDs was published. This review was prepared by the Geneva Foundation for Medical Education and Research, the Leiden University Medical Centre, the Westminster Primary Care Trust London and the WHO Department of Reproductive Health and Research. The review was updated in 2007 and published as an article in Contraception. The purpose of the systematic review was to compare different copper-bearing IUDs for their effectiveness and side effects, including evidence on whether there is an association between IUD use and pelvic inflammatory disease.

Following publication of the Cochrane Review, WHO and UNFPA convened an IUD Technical Review Committee Meeting held on 19-20 September 2006, to consider its findings and their implications for public health. The outcome and conclusions of the Cochrane Review can be found in Annex I. Attending the meeting were international experts and researchers in the field of IUDs together with the convenor and members of the ISO/TC157 WG3, the international standards technical committee responsible for developing the international standard for copper-bearing IUDs, ISO 7439, the authors of the Cochrane Review and representatives from the WHO Secretariat.
In summary, the IUD Technical Review Committee recommended that:

- The TCu380A IUD should be the preferred device for public-sector procurement on the basis of its efficacy, safety and long history of use.
- The Specification for the TCu380A IUD, originally prepared by the Population Council in 1984, should be updated to reflect general changes in medical device manufacturing practice, material availability and specification writing that have occurred since the publication of the original Specification.
- WHO and UNFPA would introduce a Prequalification Programme for TCu380A IUD manufacturers that is harmonized with the WHO Prequalification Programme for Essential Medicines. The aim of the WHO/UNFPA Prequalification Programme would be to determine whether the applicant’s product and manufacturing site(s) meet the minimum requirements detailed in the relevant ISO standards and WHO/UNFPA Technical Specification in respect of product quality and safety, production and quality management, regulatory approvals and capacity of production.

The original TCu380A IUD Specification was developed by the Population Council and formed part of the New Drug Application submission (NDA 18-680) made to the United States Food and Drug Administration (U.S. FDA). The application was originally submitted in 1981 and resubmitted in 1983. The product was cleared by the U.S. FDA for marketing in 1984.

In 2010, WHO published an updated version of the Population Council’s Specification, which took into account the many changes in the basic principles of specification writing, the publication of ISO 7439, changes in manufacturing processes, and the introduction of radiation sterilization. Following its publication the WHO/UNFPA TCu380A IUD Specification from 2010 was widely adopted internationally. Since then, UNFPA has collected significant feedback from stakeholders regarding opportunities to improve the Specification. This prompted WHO and UNFPA to initiate a revision of the 2010 document. The results are compiled in this publication, the WHO/UNFPA TCu380A Intrauterine Contraceptive Device (IUD) Technical Specification and Prequalification Guidance, 2016.

### Revision of WHO/UNFPA TCu380A IUD Specification, Prequalification and Guidelines for Procurement, 2010

The document in hand is the result of approximately two years of review and revision of the 2010 Specification by technical experts in co-operation with global stakeholders like manufacturers and health care providers, regulatory authorities, procurers and laboratories. A technical consultation was conducted with the TCu380A IUD WHO Technical Review Committee at WHO headquarters in Geneva, Switzerland in September 2013, which identified areas in the 2010 Specification requiring revision as well as opportunities for improvement of the document. In February 2014 the work of the Technical Review Committee was presented at a meeting with healthcare providers, manufacturers, and other stakeholders in New Delhi, India. Thereafter, a committee worked to continue revision of the document and it was circulated to global stakeholders for review.

Through this process it was agreed to revise the document in order to enhance usability by implementing the following general changes. In addition to the below highlighted modifications, a number of minor changes have been applied in this latest version:

- the lay-out of the Specification is amended to clearly indicate requirements for in-process and finished product;
- some parts of the Technical Specification section are presented in a tabular format;
- additional packaging and labelling requirements are specified;
- more advice is given on the requirements and methods for sterility assurance;
There is clearer differentiation between the testing and sample requirements for prequalification testing, the testing of continuing series of Lots and for isolated Lots for surveillance testing;

- the prequalification information is placed in a single chapter and product dossier and site master requirements revised; and
- the layout and content of the document is harmonized with the WHO/UNFPA documents for female and male condoms.

This revised version supersedes all previous publications since it includes important changes to the TCu380A IUD Technical Specification and the prequalification process. The changes are fully explained in each of the relevant chapters of the document. A summary of the changes is included in Annex II.

## IV Use and effectiveness of the TCu380A IUD

The TCu380A IUD is a popular, safe and very effective contraceptive. The TCu380A IUD works primarily by causing chemical changes that prevent fertilization. Studies show that the copper IUD effectively interrupts the reproductive process before implantation and pregnancy. It does not act by initiating an abortion, as has sometimes been suggested.

The percentage of women experiencing unintended pregnancy within the first year is 0.8% for typical use and 0.6% for perfect use, and the percentage of women continuing use at one year is 78%.

Once the device is inserted, the user benefits from up to 12 years of effective protection against unintended pregnancy. The recommended years of use can vary according to the guidelines and policies of a country. Health care providers should follow programme guidelines as to when the device should be removed. The method of contraception is immediately reversible upon removal.

The device does not interrupt sexual intercourse because it does not require any action on the part of the user. In addition, because the IUD is inserted in a woman’s uterus by specially trained health care providers, it is unlikely to fail due to the user’s mistake or negligence, a potential problem with many other contraceptive methods. IUDs are relatively inexpensive to manufacture and widely available.

IUDs are therefore a safe, highly effective and cost-effective method of contraception. Although there are over 160 million users globally, according to a report published by WHO/USAID/MSI, evidence suggests that the IUD remains under-utilized with uptake varying significantly across the regions of the world. The report states that some countries have wide usage while others have little or no use, especially in North America, Oceania, South Asia and Sub-Saharan Africa.

### IUD use among all married women of reproductive age:

<table>
<thead>
<tr>
<th>Region</th>
<th>Use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>33%</td>
</tr>
<tr>
<td>Scandinavian</td>
<td>18%</td>
</tr>
<tr>
<td>Asian nations</td>
<td>13%</td>
</tr>
<tr>
<td>Near East and North Africa</td>
<td>12%</td>
</tr>
<tr>
<td>European and Russian women</td>
<td>7%</td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>5%</td>
</tr>
</tbody>
</table>

Source: WHO, USAID, MSI, 2011
http://www.who.int/reproductivehealth/publications/family_planning/Long_term_contraceptive_protection_behaviour.pdf

### Recommendations for use

The two WHO documents on contraceptive use, the Medical Eligibility Criteria for Contraceptive Use and Selected Practice Recommendations for Contraceptive Use, provide guidance on when a copper-bearing IUD can be inserted. The Medical Eligibility Criteria identifies few restrictions on use based on either an individual’s characteristics or known medical conditions.

In fact, the IUD is safe and suitable for nearly all women including:

- adolescents and women over 40;
- women who have just had an abortion or miscarriage as long as there is no infection;
- women who are breastfeeding;
• women who have had pelvic inflammatory disease and are currently free from infection; and
• women who are living with established HIV infection of WHO clinical stage 1 (asymptomatic) or stage 2 (mild symptoms) and/or receiving antiretroviral therapy (ART).

If, however, a woman has an increased risk for being infected with STIs at the time of insertion, or if she is living with established HIV infection of WHO clinical stage 3 (advanced symptoms) or stage 4 (severe symptoms), she should not have an IUD inserted.

As with most contraceptive methods, there is some risk of side effects. These include the possibility of longer, heavier, and sometimes painful menstrual periods, especially during the first three to six months of use.

There are, however, very few serious health risks associated with using an IUD. Uncommonly heavier menstrual bleeding due to a copper-bearing IUD may contribute to anaemia if the woman already has low iron stores before insertion. Even rarer is the risk of pelvic inflammatory disease associated with an ongoing gonorrhoeal or chlamydial infection at the time of IUD insertion.

Complications of IUD insertion are uncommon. During insertion there is a small risk of perforation of the wall of the uterus by the IUD or the instrument used to insert it. Occasionally, an IUD is expelled. This is usually harmless unless a woman does not notice it and becomes pregnant.

There are a number of misperceptions regarding the use of IUDs that have been clarified in the WHO documents on contraceptive use detailed in WHO’s Family Planning: A Global Handbook for Providers which provides evidence-based guidance which clarifies that:

- Use of an IUD rarely leads to pelvic inflammatory disease (PID);
- IUDs do not increase the risk of contracting sexually transmitted infections (STIs) including human immunodeficiency virus (HIV), which causes AIDS;
- IUDs do not make a woman infertile;
- IUDs do not cause birth defects;
- IUDs do not cause cancer;
- IUDS do not move to the heart or brain;
- IUDs do not cause discomfort or pain for the woman during sex; and
- IUDs substantially reduce the risk of ectopic pregnancy compared with the risk of using no contraception.

The copper-bearing IUD is an appropriate contraceptive for the postpartum period. A recommendation in the 2008 update of the WHO Selected Practice Recommendations for Contraceptive Use states that a woman can have a copper-bearing IUD inserted up to 48 hours after delivery, including immediately after delivery of the placenta. If the delivery is by caesarean section, a copper-bearing IUD can be placed after delivery of the placenta, before closing the uterus. For IUDs specifically manufactured and labeled for postpartum insertion, deviations from the specifications regarding length of string and dimensions of the inserter are permitted if they can be clinically justified.

If the copper-bearing IUD is not inserted within 48 hours after delivery, then a woman can have the IUD inserted at four weeks postpartum or thereafter, provided her menstrual cycle has returned. If it has not returned, the IUD can be inserted if it can be determined that the woman is not pregnant.

IUDs do not protect against contracting STIs, including HIV. To effectively prevent contracting an STI and/or HIV infection, the correct and consistent use of condoms is recommended in addition to using IUDs.
References


Chapter 1

WHO/UNFPA TCu380A IUD Prequalification Programme
1.1 Background

The United Nations, through its procurement, supplies medicines and health care products to countries throughout the world providing access to a choice of products of acceptable quality, safety and efficacy.

The aim of the WHO/UNFPA TCu380A IUD Prequalification Programme is to ensure that the applicant – hereafter referred to as the manufacturer – meets the minimum requirements set out in the relevant ISO standards and in this WHO/UNFPA TCu380A IUD Technical Specification and Prequalification Guidance, 2016 document, in respect to product quality and safety, production and quality management, regulatory approval and production capacity. TCu380A intrauterine devices (IUDs) that are produced at manufacturing sites prequalified by the WHO/UNFPA Prequalification Programme, have been found in principle to be acceptable for procurement by United Nations agencies.

The WHO/UNFPA Prequalification Programme involves the following key activities:

- evaluation of documents submitted in response to an invitation for Expression of Interest (EOI);
- inspection of each manufacturing site per product;
- product testing;
- review of testing and inspection reports to make a decision about the acceptability of each product and its specific manufacturing site; and
- periodic reassessment of the prequalification status of products and manufacturing sites.

1.2 Objectives

The overall objective is to implement a programme to prequalify TCu380A IUDs of assured quality at specific manufacturing sites for procurement by United Nations agencies. Specific objectives are to:

- broaden and improve the quality of the supplier base for TCu380A IUDs that are deemed acceptable, in principle, for procurement by United Nations agencies; and
- maintain and publish a list of prequalified products and manufacturing sites.

1.3 Transparency and Confidentiality

UNFPA assessors and inspectors will treat all information to which they will gain access during the evaluations and inspections, or otherwise, as confidential and proprietary to UNFPA or parties collaborating with UNFPA, in accordance with the terms set forth below.

UNFPA contracted technical experts will take all reasonable measures to ensure:

- that confidential information is not used for any other purpose than the evaluation/inspection activities described in this document; and
- that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

By participating in the Prequalification Programme, the manufacturer agrees to allow full access to:

- any of the facilities that are in any way involved in the production of the product(s) concerned; and
- all documentation related to that production.

If such access is not provided, the manufacturing site and specific products cannot be prequalified.

Any evidence of fraud or serious omissions by the manufacturer in the initial assessment procedure will lead to termination of the site inspection.

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During the prequalification process, UNFPA and its assessors and inspectors cannot accept any gifts from the companies they visit. UNFPA requires that manufacturers do not make any offers of gifts of whatever value.

1.4 Eligibility to Participate

The Prequalification Programme is intended for manufacturers of TCu380A IUDs that undertake the processes of moulding, assembly, sterilization and packaging, as specified by UNFPA in the call for an Expression of Interest (EOI), referred to below.

One or more of these processes may be carried out on a contract basis, but the manufacturer retains overall responsibility for product quality.

The Prequalification Programme does not apply to suppliers engaged only with testing or repackaging.

1.5 Fees

At present, UNFPA covers expenses related to assessments, inspections and product testing. Manufacturers are responsible for their own costs related to providing the necessary information required under the Prequalification Programme. If reinspection or retesting is required during a single evaluation period, the manufacturer may be requested to cover the costs associated with this.

The inspection team is paid by UNFPA to inspect the facilities, and the members are reimbursed for their hotel and transport expenses by UNFPA. The manufacturer will not pay for hotel accommodation or make any payments for, or to, the inspection team. The manufacturers may be requested to assist in making reservations at an appropriate hotel and for local transportation to and from the airport or station, and to and from the inspectors’ hotel to the facilities.

At the time of publication, the process is conducted by UNFPA free of charge. UNFPA reserves the right, however, to charge a fee on a cost-reimbursement basis.

1.6 Language

The official language of the programme is English. All documents submitted as part of an application for prequalification shall be in English. If the original of any required document is not in English, the manufacturer must submit a copy of the original, plus a certified translation into English. All reports issued by UNFPA will be in English.

Inspections will be conducted in English, where necessary with the aid of an interpreter. It is the responsibility of the manufacturer to advise UNFPA and for UNFPA to agree when an interpreter is required in advance of an inspection. The interpreter will be selected by UNFPA in advance of the inspection.

1.7 Technical Experts Hired by UNFPA

Profile

Document assessments and inspections are carried out by technical experts appointed by UNFPA. The technical experts are selected through an international competitive bidding process to select individuals that have documented qualifications, detailed knowledge of the process for manufacturing IUDs, experience in auditing and quality management systems and specific experience inspecting IUD manufacturing sites.

One member of the team will be designated by UNFPA as the “lead inspector” and will be responsible for the coordination of inspection activities and production of the report. The team will include staff member(s) from UNFPA. UNFPA will advise and seek the involvement of the national competent body in the on-site inspection.

Conflict of Interest

Before undertaking the work, each technical expert will be required to declare any conflict of interest. If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), he/she will discharge his/her functions exclusively as adviser to UNFPA. In this connection each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete and that he/she will immediately notify UNFPA of any change in this information.

UNFPA will advise the manufacturer in advance of the composition of the team performing the document assessment and site inspection. The curricula vitae of technical experts can be provided upon request. The manufacturer then has the opportunity to express concerns regarding any of the technical experts performing the prequalification evaluation to UNFPA. If such concerns cannot be resolved in consultation with UNFPA, the manufacturer may object to a team member’s participation in the documentation assessment and/or site inspection.
Such an objection must be made known to UNFPA by the manufacturer within 10 days of receipt of information on the composition of the proposed team. In the event of such an objection, UNFPA may reassign the activities to be undertaken by different technical expert(s).

1.8 Prequalification Process

1.8.1 Expression of interest
Invitations to interested parties to submit an Expression of Interest (EOI) are published at regular intervals on the UN Global Marketplace (UNGM), available from: www.ungm.org. The invitation is open and transparent. It invites manufacturers, to submit an EOI for the products listed in the invitation. The manufacturers should submit their EOIs to the UNFPA focal point with the relevant information. The manufacturers will be given a specified period to submit their responses from the time of publication of the advertisement.

In situations of high public health concern, as determined by WHO, UNFPA may also directly invite relevant parties to submit their product for assessment by UNFPA under this procedure without publication of an invitation for EOIs.

Data and information to be submitted
When submitting an EOI for product evaluation, the manufacturer should send to the UNFPA focal point the following:

- A covering letter expressing interest in participating in the UNFPA prequalification procedure and confirming that the information submitted in the Product Dossier (PD) and Site Master File (SMF) summary is complete and correct (See Annex IV).
- Product Dossier checklist and Product Dossier in the format specified.
- Site Master File checklist and a Site Master File summary for each manufacturing site listed in the Product Dossier, in the format specified.
- 10 product samples, as examples of products produced.
- A schedule of IUD production during the prequalification evaluation period.
- Copies of all current certifications and accreditations, all manufacturing licenses, registrations held, and a copy of the company registration. Verification of certification will be carried out at the time of inspection.

A Product Dossier (PD) is prepared for the product seeking prequalification. The PD shall be prepared in accordance with the requirements in Annex IV.

A Site Master File (SMF) summary is prepared by the manufacturer from the documented quality management system. The SMF must contain specific factual information regarding manufacturing processes for each manufacturing site and be prepared in accordance with Annex IV. If only part of a manufacturing operation is carried out at a site, the SMF summary needs to describe only the operations carried out at the site.

Format and process for submitting documentation
Documentation prepared in accordance with the guidance given in Annex IV, with the exception of the covering letter, shall be submitted in electronic format in the form of a CD-ROM, USB, or equivalent. Electronic submissions via email will not be accepted.

Hard copy applications may be submitted in addition to the electronic version.

The letter of application, a device containing the electronic documents, and the products samples shall be sent in a single envelope to the below address:

UNFPA, Procurement Services Branch
Attn: IUD Prequalification Programme
Marmorvej 51
2100 Copenhagen
Denmark

UNFPA will receive and record the EOI from each manufacturer and issue an acknowledgement of receipt. UNFPA reserves the right to accept or reject late applications. Applications not prepared in accordance with the format requirements detailed in Annex A will not be accepted for review.

For further information on how to submit your application, please contact procurement@unfpa.org.

1.8.2 Document assessment

Initial screening of documentation
UNFPA will aim to screen the submitted documentation within 30 days of the closing date for response, to ascertain whether it contains all the required information. If the submission is incomplete, the manufacturer will be informed and requested to complete the dossier within a specified time period. If the document remains
incomplete, it may be rejected.

Dossiers that are considered complete as the result of the administrative screening will be retained by UNFPA for evaluation.

**Assessment of the product dossier and site master file**
The aim of the assessment of the submitted documentation will be to determine whether the manufacturer meets the minimum requirements set out in the relevant ISO standards and this WHO/UNFPA TCu380A IUD Technical Specification in respect of product quality and safety, production and quality management, regulatory approval and capacity of production.

UNFPA aims to complete the assessment of the Product Dossier and the Site Master File summary within a specified time period (90 days) of the closing date for receipt of responses.

The assessment of the submitted documentation will be done in accordance with standard operating procedures (SOPs) established by WHO/UNFPA for that purpose. To ensure uniformity in evaluation and timeliness of assessment activities, UNFPA will, if needed, provide training to the assessors.

In making its assessment, UNFPA may take into account information submitted by the manufacturer during previous applications that may be in UNFPA’s possession, including results from previous site inspections and laboratory test results on products produced by the manufacturer.

UNFPA aims to advise the manufacturer of the outcome of the assessment of documentation within 30 days after its completion. If applications are found to be in conformance with the UNFPA requirements, inspection of the manufacturing site will be scheduled.

**1.8.3 Site inspection**
UNFPA will plan and coordinate inspections at the relevant manufacturing sites to assess the manufacturing process and the product and quality management systems for conformance with general and performance requirements of the WHO/UNFPA TCu380A IUD Technical Specification and Good Manufacturing Practice (GMP). The inspection shall verify manufacturer conformance with, but not limited to, the latest editions of the following international standards:

- ISO 7439 Copper-Bearing Intrauterine Contraceptive Devices - Requirements, Tests.
- ISO 14001 Environmental Management
- ISO 14971 Medical Devices - Application of Risk Management to Medical Devices.
- ISO 10012 Measurement management systems - requirements for measurement processes and measuring equipment.
- ISO 10993 Biological Evaluation of Medical Devices - relevant sections as specified ISO 10993-1.
- ISO 11135 Medical devices - Validation and Routine Control of Ethylene Oxide Sterilization - relevant sections as specified in ISO 11135-1.
- ISO 11137-3 Guidance on Dosimetric Aspects.
- ISO 11607 Packaging for Terminally Sterilized Medical Devices - relevant sections as specified in ISO 11607-1.
- ISO 19011 Guidelines for Quality and/or Environmental Management Systems Auditing.

The manufacturing site shall be certified to ISO 14001 by an accredited certification body and, based on this, have an Environment Management System (EMS) in place. At time of inspection, ISO 14001 certification will be checked and auditors may review certain aspects of the environmental policies and procedures. However, UNFPA will not conduct ISO 14001 audits.

**Scope and scheduling**
Prior to the inspection, the manufacturer will be informed of the scope of the inspectors’ planned activities. The key components of the inspection are described in the guide.
for inspection of manufacturing sites included as Annex V of this document. The inspection will not be limited to these components. IUD manufacturing sites vary widely in size and scale, equipment and processes, and inspectors will have to use their expertise and knowledge of IUD manufacture to adapt the table to the specific situation at each site.

Manufacturers must be prepared to show the inspectors all aspects of the manufacturing process, including sites for compounding, injection moulding, sterilization and records and data that relate to the production of the IUDs. Where necessary, manufacturers must organize access to facilities of contractors who undertake off-site activities such as moulding, compounding and sterilization. In addition, the inspectors may request copies of documents presented as evidence during inspection and may request permission to make a photographic record of the inspection, subject always to consideration of confidential information.

Any evidence of fraud or serious omissions by the manufacturer during the inspection will lead to termination of the site inspection.

UNFPA aims to advise the manufacturer of the date of inspection at least 30 days in advance. UNFPA and the inspectors will make efforts to accommodate reasonable requests made by the manufacturer and national regulatory authorities to change the dates of the inspection.

1.8.4 Product testing

Products will be sampled for independent testing prior or subsequent to the inspection under the supervision of, or by, an independent sampler appointed by UNFPA or by the inspectors at an appropriate point during the site inspection.

As a component of their prequalification application manufacturers shall submit a copy of their production plan for the coming year to enable UNFPA to communicate the number of samples from each production lot the manufacturers should retain for prequalification testing and/or to schedule the inspection during a time when ample lots will be available for sampling.

Sampling and testing will be conducted in accordance with the requirements detailed in the WHO/UNFPA TCu380A IUD Technical Specification. All product testing will be undertaken by independent test laboratories selected by UNFPA, of defined and documented competence and experience, as demonstrated by accreditation to the current ISO 17025 standard with testing of IUDs within the scope of its accreditation.

The sample will be packed and sealed by the inspector or the independent sampler as appropriate. The inspectors may take the sample with them or arrange for the manufacturer to have the sealed box sent to the selected laboratory by courier at UNFPA’s expense. The manufacturer will be provided with a copy of this test report.

1.8.5 Reporting and decision to prequalify

At the conclusion of the inspection, the inspectors will prepare a brief written summary report outlining the key non-conformities and observations discussed with the manufacturer during the site inspection. This report will be provided to UNFPA with a copy to the manufacturer. Manufacturers should not submit corrective actions to UNFPA in response to this summary report, but only in response to the official inspection report that is issued. The official inspection report prepared by the inspection team will be issued by UNFPA to the manufacturer four to six weeks following the inspection. The report will indicate one of the following recommendations:

- Prequalify the TCu380A IUD manufactured at a specific site without conditions. This will only be the case when there is no evidence that corrective action is required.
- Require the manufacturer, where deemed necessary, to undertake specified corrective and preventive action(s) (CAPA).
- Determine that product and manufacturing site is ineligible for prequalification (without any requirement for corrective action being offered). This will not, however, preclude the manufacturer from re-submitting an application in response to future invitations for EOI.

The inspection report may contain non-conformities and observations. Non-conformities are classified as major or minor. A manufacturer that receives a major non-conformity cannot be prequalified and if already prequalified, status may be suspended. A major non-conformity will require submission of corrective and preventative actions and a possible re-inspection. Minor non-conformities require corrective and preventative action to be submitted to UNFPA by the manufacturer in the stated period in order to achieve or maintain prequalification. Observations made by the inspectors are intended to highlight opportunities to improve quality management practices. It is strongly recommended that manufacturers consider acting upon any observations made, but prequalification is not dependent upon this.
Corrective and preventive action (CAPAs) submissions should be submitted to UNFPA electronically in response to the official inspection report. Evidence of action shall be provided. Evidence of actions taken should be supplied to UNFPA in the form of SOPs, pictures, or other appropriate formats. The files submitted shall be organized and clearly labelled. Each manufacturer will be permitted two rounds of CAPA reviews. The first submission of corrective and preventive actions shall be in possession of UNFPA within 90 days of receipt of the official inspection report unless otherwise agreed by UNFPA. If a manufacturer has not successfully addressed all non-conformities raised during the inspection following the second CAPA review, the manufacturer may be asked to submit a fresh expression of interest for prequalification. The expression of interest should only be submitted when the manufacturer demonstrates compliance with the Prequalification Programme requirements. Any exceptions to this will be evaluated on a case-by-case basis.

UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the manufacturer is:

- not able to provide the required information; and/or
- unable to implement the corrective actions in a specified time period; and/or
- if the information supplied is inadequate to complete the quality assessment process.

Each manufacturer will receive a letter from UNFPA informing the manufacturer of the outcome of the quality assessment process. UNFPA aims to inform the manufacturer of the results of the process within 30 days of receipt of all final reports.

Manufacturers will verify the final report that is produced for accuracy. In the event of any disagreement between a manufacturer and UNFPA, an SOP established by UNFPA detailing the handling of appeals and complaints will be followed to discuss and resolve the issue.

The ownership of any of the reports produced during the course of, or as the result of the assessment of documentation, product testing and inspection of the manufacturing site, lies with UNFPA. Thus, UNFPA shall be entitled to use and publish such reports and/or a summary of a report, subject always, however, to the protection of any commercially confidential information of the manufacturer(s).

Confidential information may include:

- confidential intellectual property, “know-how” and trade secrets (including, e.g. formulas, processes or information contained or embodied in a product, unpublished aspects of trademarks and/or patents);
- commercial confidences (e.g. structures and development plans of a company).

Notwithstanding the above points, UNFPA and WHO reserve the right to share a summary and/or the full evaluation and inspection reports with the relevant authorities of any interested Member State of UNFPA and/or WHO.

Listing of prequalified IUDs and manufacturing sites
Once UNFPA is awarded a positive prequalification decision, the product as produced at the specified manufacturing site(s) will be listed on the websites for UNFPA and WHO.

1.8.6 Maintenance of prequalification status
Once the product and corresponding manufacturing site(s) are included in the list of prequalified TCu380A IUDs, the manufacturer shall be required to inform UNFPA, within four weeks, of any matter that affects the information on which approval was based. This includes prior notification of any intended changes in the manufacturing site and manufacturing process. It may also include, but is not limited to:

- change of premises
- change in production and testing equipment
- change in senior management
- product recalls
- change in certifications or licences held by the manufacturer
- reports of adverse events
- change in design
- change in suppliers of raw materials
- change in specification of raw materials
- change in raw material processing
- change in production
- change in packaging
- change in sterilization processes
- new information about shelf life.

It is the manufacturer’s responsibility to provide UNFPA with the appropriate supporting documentation, including appropriate test and validation protocols and other relevant documents, all referring to relevant parts of the Product Dossier and Site Master File summary, to prove that the implementation of any intended variation will not have an
adverse impact on the quality of the product that has been prequalified. UNFPA will undertake an evaluation of variations according to established UNFPA guidelines and SOPs and communicate the outcome to the manufacturer. Conformance with the requirement to report changes will be checked during the inspections carried out by UNFPA.

**Periodic monitoring of the quality of the products produced by prequalified manufacturing sites**

At periodic intervals UNFPA may, through an independent sampler, take random samples of TCu380A IUDs produced by listed manufacturers. The sample size taken and range of tests performed will be in accordance with the current WHO/UNFPA TCu380A IUD Technical Specification.

All product testing will be undertaken by independent test laboratories selected by UNFPA. UNFPA selects laboratory based documented evidence of accreditation to the current ISO 17025 international standard with testing of IUDs within the scope of their accreditation as well as demonstrated capacity to perform testing against the WHO/UNFPA TCu380A IUD Technical Specification. In the event of failure of the product to meet the established requirements for testing, UNFPA will investigate the problem and communicate this to the manufacturer.

UNFPA may request reports from consumer or regulatory bodies, or from other procurement agencies, relating to the quality and supply of the prequalified TCu380A IUD.

Complaints concerning prequalified TCu380A IUDs communicated to UNFPA will be investigated in accordance with an SOP established by UNFPA for that purpose. After investigation UNFPA will provide a written report of the complaint investigations, including recommendations for action, to the manufacturer. UNFPA will require evidence of effective action taken, where relevant.

UNFPA will make the report available to the appropriate authorities of the country where the manufacturing site is located when necessary in the interested of public health, subject always to consideration of commercially confidential information, as referred to earlier in this chapter. UNFPA reserves the right to make such reports public, if it considers this to be of public health importance. In addition, UNFPA reserves the right to share the full report and/or recommendations for action with WHO and relevant authorities of interested Member States of the World Health Organization.

At periodic intervals UNFPA may request a summary of the statistical analysis of TCu380A IUD production from the manufacturer for demonstration of continued capability to manufacture to the WHO/UNFPA TCu380A IUD Technical Specification. This may be accompanied by a request for selected evidence from management review, risk management, production, measurement and analysis and other records.

**Reassessment of prequalified manufacturing sites**

UNFPA aims to undertake a requalification assessment of TCu380A IUDs manufactured at a specific site at intervals of no more than three years. Such reassessments will consist of the same processes carried out during the initial prequalification of the manufacturer.

Reassessment may also be required in the following situations:

- if the UNFPA prequalified manufacturer reports to UNFPA that a field complaint has been received that resulted in a product recall. Prequalified manufacturers must report all such events to UNFPA
- if the TCu380A IUD supplied by the manufacturer are considered by UNFPA or one or more of the other United Nations agencies not to be in conformance with the agreed WHO/UNFPA TCu380A IUD Technical Specification
- if a complaint considered serious in nature has been received by UNFPA or one or more of the other United Nations agencies or organizations
- if there is a significant change.

All relevant information including the reassessment of submitted documentation and the requalification site inspection report, together with monitoring information, will be considered by the designated UNFPA official, and a decision will be made to:

- maintain the TCu380A IUD and its manufacturing site on the list of prequalified products without need for corrective actions and/or
- maintain the prequalification status of the TCu380A IUD and manufacturing site with a requirement for corrective actions and, where agreed to by UNFPA, further product testing and/or site inspection and/or
- suspend prequalified status.

UNFPA will de-list any prequalified product and manufacturing site if submitted information is subsequently found to be incorrect or fraudulent.
Chapter 2

Essential Elements of IUD Quality Assurance
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Essential Elements of IUD Quality Assurance

2.1 Introduction

The objective of this chapter is to describe the essential elements of IUD quality assurance with specific reference to the TCu380A IUD. This chapter introduces concepts and topics that are elaborated on in following chapters of the document. This information serves as a guide to incorporating quality assurance into your own procurement of TCu380A IUDs and covers key considerations for:

- product specification
- manufacturer qualification
- monitoring supplier performance.

The quality assurance measures described in this document are designed to protect both the procuring agency and the end-user since:

- There may be substantial differences in the quality of IUDs produced by different manufacturers. Quality may also drift over time during the production of a Lot or vary between Lots made at different times.
- IUDs are relatively stable products but they are supplied sterile and it is essential that the packaging is capable of maintaining the specified sterility assurance level even if the products are stored under adverse conditions.
- A poor-quality product may fail to provide adequate contraceptive protection, be spontaneously expelled from the uterus (potentially leading to unplanned pregnancy), cause infection, cause uterine perforation or cause other adverse events.
- A poor-quality product will quickly destroy the credibility of any IUD promotion programme.
- A poor-quality product can cause a political, financial, logistical and social crisis since funds would have to be found for medical interventions to potentially remove all defective devices from affected women and treat any adverse outcomes associated with the use of the device.

2.2 Standards

What is a standard?

Standards are published by national, regional and international standards bodies to establish the minimum performance, quality and safety requirements for products that are made, imported and sold within a particular country or region. They are usually generic in nature and not design restrictive.

Standards also specify standardised test methods to be used when testing products for quality assurance and conformance purposes. The test methods published in standards have normally been subjected to extensive validation studies including inter-laboratory trials to establish their reproducibility, accuracy and reliability under a wide range of operating conditions.

Standards not only cover specific products but also specify procedures and processes such as quality management system requirements, methods of sterilization, requirements for conducting risk assessments, statistical sampling procedures and many other activities essential for the production of safe and effective products. This is often achieved by citing other standards and reference documents that need to be sourced in order to understand the requirements of the standard.

Who develops standards?

Standards are developed by voluntary standards committees consisting of manufacturers, major purchasers, consumer groups, research organizations, testing laboratories, trade associations and other interested parties. In the case of medical devices such as IUDs, national regulatory bodies, public health experts, international procurement agencies and clinicians may also be represented on the standards committees. The principal international standards authority is the International Organization for Standardization (ISO), a worldwide federation of national standards bodies responsible for drafting international standards based on the best available evidence and practice.

ISO Technical Committee ISO/TC 157 Non-systemic contraceptives and STI barrier prophylactics is responsible for developing international standards for non-systemic barrier contraceptives which include male and female condoms, diaphragms and IUDs. ISO/TC 157 has a membership of approximately 25 countries with representatives drawn from a wide range of interested parties including manufacturers, test laboratories, regulatory bodies and consumers’ representatives. WHO, UNFPA and other partner agencies work with this committee.

What is the standard for TCu380A IUDs?

The International Standard for copper bearing IUDs is ISO 7439. ISO 7439 is a generic standard that covers all copper bearing IUDs. This standard includes requirements for:
• appropriate dimensions, materials of construction, performance and storage requirements to ensure acceptable contraceptive effectiveness and, in the case of barrier contraceptives, effective STI protection with minimum risk of adverse reactions and side effects
• adequate product protection against potentially harsh environmental conditions that could degrade the product or compromise its sterility
• appropriate packaging to protect the product and, in the case of IUDs, maintain sterility
• information for the healthcare professional and product users on how to store and use the device
• in the case of IUDs, information to be passed to the recipient of the device providing instructions on what to do in the event of an adverse reaction, expulsion or other event.

The current edition of ISO 7439 can be purchased from national standards organizations or from:

International Organization for Standardization (ISO)
ISO Central Secretariat
1 rue de Varembé, Case postale 56
CH-1211 Geneva 20
Switzerland
Telephone: + 41 22 749 01 11
Telefax: + 41 22 733 34 30
Email: central@iso.org.
Website: http://www.iso.org

Copies of the standard can also be downloaded (for a fee) from the ISO website and the websites of other national standards organizations.

A minor revision to ISO 7439 was published in 2015 by ISO/TC 157. This revision corrected a number of minor errors in the clauses relating to clinical trials including clarification of the purpose of using control IUDs in studies. The changes do not impact on the general design and performance requirements for IUDs.

How are standards used in regulation and procurement?
Conformance with standards is voluntary but in many cases procurement bodies, governments and/or regulatory bodies make conformance mandatory. In the case of medical devices, demonstrating conformance with one or more key standards is normally required for successful procurement or registration of a product for a country or region. The manufacturers’ quality management systems must also have to be independently certified to an appropriate standard such as ISO 13485 Medical devices - Quality management systems - Requirements for regulatory purposes.

The design, requirements, testing, manufacturing and quality assurance of a specific medical device is therefore likely to be covered by a number of standards, each addressing different aspects of the device, the manufacturing process and the quality management system.

2.3 Specifications

What is a Specification?
A specification is a statement of the buyer’s requirements and covers all the product attributes necessary for buyer acceptance. For procurement, the purchaser must provide a specification that details the characteristics and quality of the product to be manufactured and specify the tests by which the quality can be verified. These include the essential general and performance requirements as well as discretionary design requirements. A specification includes or references the test methods to be used to verify the quality of a product and may demand a different level of quality than a published standard requires.

WHO/UNFPA TCu380A IUD Technical Specification

The WHO/UNFPA Technical Specification detailed in Chapter 2 of this document is based, where appropriate, upon ISO 7439. The ISO 7439 standard is generic in nature and applies to all copper bearing IUDs. However, the WHO/UNFPA Technical Specification is specific to the TCu380A IUD. For example, whereas the WHO/UNFPA Technical Specification gives all the critical frame dimensions for the TCu380A device, ISO 7439 only specifies the maximum frame length and width. The WHO/UNFPA Technical Specification, if used in conjunction with the prequalification procedure (see Chapter 1) and adequate procurement procedures, should help ensure that a quality product is manufactured, purchased and distributed to the consumer.

WHO and UNFPA have prepared a Technical Specification that is internationally designed and accepted for the bulk procurement of TCu380A IUDs. The Technical Specification can be adopted by any body seeking to procure TCu380A IUDs.

2.4 Regulatory Authorities

Copper bearing IUDs are classified and regulated differently by various regulatory agencies around the world. These bodies license drugs and medical devices for use in a particular country or region. In addition, some carry out or commission audits and product testing. They generally have the power to refuse to license and recall products as well as close manufacturing sites in the event of continued
non-conformance with their regulations. Most countries have their own regulatory procedures, which should be updated in accordance with the published standard. It is always advisable to review national regulatory policy and guidelines before importing IUDs into a country.

In the EU, copper bearing IUDs are classified as Class III medical devices with ancillary medicinal substance. Approval to market the product is obtained through a CE Mark submission to an appropriate Notified Body. The Notified Body is required to consult with a Competent Authority concerning the safety and usefulness of the medicinal substance. Since the copper is the active medicinal substance this can raise issues relating to the control, manufacture, stability and purity of the copper components. Manufacturers seeking a CE Mark for a copper bearing IUD will have to satisfy the Competent Authority that they have acceptable levels of control over the source of the copper components and can provide data to confirm the quality and purity of these components.

For manufacturers residing outside the EU an authorised representative has to be appointed to supply the information when required.

In the USA copper bearing IUDs are classified as combination products and are regulated as drugs by the FDA Center for Drug Evaluation Research (CDER). Approvals are via the New Drug Application route which generally requires robust clinical studies and appropriate safety studies to support the effectiveness and safety of the device.

It is important to work closely with national regulatory authorities and inform them of the procurement procedures and testing protocols that will be used to verify the quality of the IUDs before they are shipped to the country.

2.5 Prequalification of Products and Manufacturing Sites

Prequalification is a procedure designed to assess the capability of a manufacturer to supply a quality product before a contract is awarded to reduce the risk of awarding a contract to a manufacturer that is unable to meet the quality requirements. The purpose of prequalification is to protect both the buyer and the consumer. It is recommended that the purchasers buy only from manufacturers that are prequalified under the WHO/UNFPA Prequalification Programme which verifies that the manufacturers have the potential capacity, capability and quality infrastructure to produce the required products in the specified time-frame. This is demonstrated and conformity confirmed during prequalification and throughout the re-qualification cycles.

An effective Prequalification Programme: excludes manufacturers that do not have the capability of producing IUDs that meet the performance requirements of the WHO/UNFPA TCu380 IUD Technical Specification and ISO 7439;

- provide evidence of product and service conformity with the specification and relevant standards
- maximizes the likelihood that the product quality will be consistent throughout the order
- verifies that the manufacturer has the quality assurance and management system to control the properties and parameters stated in the general requirements of the WHO/UNFPA TCu380A IUD Technical Specification that cannot be practically checked on the finished product
- ensures that the manufacturer has the physical capacity to make the goods according to the delivery schedule
- saves time and expense when dealing with orders and deliveries later on
- eliminates the least competent and least reliable suppliers.

WHO/UNFPA Prequalification Programme

WHO and UNFPA run a Prequalification Programme for TCu380A IUDs. WHO is the normative leader of this programme, while implementation is carried out by UNFPA. The WHO/UNFPA Prequalification Programme involves the following key activities:

- evaluation of documents submitted in response to an invitation for Expression of Interest (EOI)
- inspection of the manufacturing site
- product testing
- review of testing and inspection reports to make a decision about the acceptability of each manufacturer
- Periodic reassessment of the prequalification status of the product and manufacturing sites.

Full details of the WHO/UNFPA Prequalification Programme for the TCu380 IUD are given in Chapter 3. This Programme is harmonized with the WHO Prequalification Programme for essential medicines and other reproductive health products. A list of prequalified manufacturers is maintained by UNFPA and is available on the WHO and UNFPA prequalification websites. It is strongly recommended that only prequalified manufacturers are used for the procurement of IUDs for public sector distribution.
2.6 Manufacturer Quality Management System

2.6.1 Medical Devices ISO 13485 certification

To become prequalified, a manufacturer must have an audited and well documented quality management system implemented, which is certified to ISO 13485.

ISO 13485 specifies the requirements for quality management schemes for medical device manufacturers. The standard is based on ISO 9001 - the foundation standard for quality management systems.

The essential components of an ISO 13485 quality management system are:

- a process approach that consistently delivers product meeting all its requirements
- supporting criteria and methods to ensure the operation and control of these processes are effective
- available fully competent and qualified people, equipment, infrastructure and other resources to support the processes
- monitoring, measurement and analysis of these process
- actions to achieve planned results and maintain the effectiveness of the processes.

Supporting these essential components there will be:

- documented quality objectives
- documented management responsibilities
- documented training procedures
- documented process and quality assurance procedures
- documented record-keeping
- remedial action in case of product quality problems.

TCu380A IUDs are sterile products. The devices must therefore be manufactured in a controlled environment so that the bioburden on the products prior to terminal sterilisation can be controlled. Periodic monitoring of the environment is required and UNFPA recommends that bioburden levels are measured on every Lot using a validated procedure prior to sterilisation. Sterilization must be carried out in accredited sterilization facilities in accordance with the appropriate standards for the method being used. If, as is usually the case, sterilization is contracted out, then the IUD manufacturer remains responsible for ensuring that the sterilization procedure has been fully validated, that there are procedures in place to monitor and control the sterilization procedure, and that the products have been subject to the appropriate conditions to achieve the specified sterility assurance level.

Periodic audits by the IUD manufacturer of the sterilization facility are necessary to ensure that everything is in order.

2.6.2 Environmental and social policies

UNFPA requires the manufacturer to establish environmental and social policies. It is UNFPA’s intention to incorporate environmental and social criteria considerations into the evaluation process, such as adherence to Global Compact requirements. http://www.unglobalcompact.org/. UNFPA encourages suppliers to join the UN Global Compact and to look into further ways to reduce their environmental impact.

At time of tender, the following documentation is required:

- environmental certifications such as ISO 14001
- documentation that the manufacturer is complying with all local environmental laws
- manufacturers’ environmental policy, including energy saving plan and air pollution reduction plan
- manufacturers’ waste management policy, including waste saving plan
- continual environmental improvement plans

All of the above shall be in line with ISO 14001.

2.6.3 Certification and accreditation schemes

A number of organizations offer certification to the various standards required for medical device manufacture. In most countries, these organizations are private companies, although in some cases there are government agencies. To determine consistency of manufacturing, the certification schemes generally focus on the essential components given above and seek information supporting effective implementation from available documentation. They do not assess the safety and efficacy of the product in an ISO 13485 audit. The certifying organizations can be an appropriate national authority or a body designated by a national authority. In Europe the certifying organizations for medical devices are known as Notified Bodies, designated and audited by a competent authority to undertake conformity assessments of medical devices. Information on certification organizations can be found on the internet and the certification status of manufacturers can be confirmed through the certification organizations’ websites.

The ISO certification body shall be accredited for the respective ISO audit. If there is no accredited national or regional certification body for e.g. ISO 13485 accreditation, a certificate issued by a competent certification body might be acceptable at the discretion of UNFPA.
2.7 Quality Control and Monitoring

Procuring WHO/UNFPA prequalified products from prequalified sites that have been produced against the WHO/UNFPA Technical Specification for TCu380A IUDs can provide procurers with a high degree of confidence in their product. However, all process control within a manufacturing operation is statistically based and even in the most highly regulated and tightly controlled manufacturing environments, products at the margins of acceptability and a bit beyond will occasionally get through. Given the consequences of purchasing and distributing poor quality IUDs in the public sector, purchasers may want to carry out additional third-party testing to ensure product quality prior to products being shipped. Testing should only be done by laboratories that comply with the criteria given in Section 2.7.3.

2.7.1 Conformity assessment

Conformity assessment is a regime of testing to verify that a Lot complies with The Specification. Conformity testing can include independent Lot-by-Lot, surveillance, random Lot, skip Lot testing etc. This document provides specific guidance for prequalification testing, production testing and surveillance testing.

Prequalification testing

Prequalification testing is testing being carried out for prequalification purposes and typically has larger samples sizes. When testing is being conducted for prequalification purposes, samples sizes and technical requirements indicated in Chapter 3, Table 3.1 should be used.

Production testing

The sampling plan given for production testing in the WHO/UNFPA TCu380A IUD Technical Specification was designed to minimise the amount of testing required while providing a high level of protection against poor quality Lots being accepted. In part this has been achieved by incorporating a requirement to increase the sample size if at any time two Lots are rejected in a consecutive series of five or fewer Lots. This is an example of an application of the switching rules specified in ISO 2859-1. The switching rules were designed to protect the consumer by switching to tightened inspection should a deterioration in quality be detected, as well as provide an incentive to reduce inspection costs by switching to reduced inspection should consistently good quality be achieved. In the case of IUD manufacture for public sector distribution, many of the requirements for switching to reduced inspection cannot necessarily be guaranteed in advance. Only the switch between normal and tightened inspection has therefore been included in Table 3.2.

Bulk purchasers who wish to conduct Lot-by-Lot can use these sampling plans. It is recommended that manufacturers who conduct Lot-by-Lot testing should review accumulated data to access quality trends. Significant (in excess of 5%) levels of Lot failures are usually indicative of marginal or poor quality.

Surveillance testing

Surveillance testing is testing that is conducted on fewer than five Lots of IUDs on a periodic basis. The switching rule is not applicable for surveillance testing due to the small numbers of Lots being evaluated at any one time. For this reason sample sizes have been increased to maintain an adequate level of consumer protection.

2.7.2 In-Country Confirmatory testing

Confirmatory testing is testing carried out on receipt of a product in a country. In some circumstances local regulatory bodies or government agencies may require this. Local regulatory bodies must take into account the results of previous testing before reaching any conclusions about quality. Confirmatory testing may also be done to confirm that the product has not undergone any deterioration in properties during shipment.

Confirmatory testing can be restricted to selected Lots, chosen at random, from a shipment or consignment. It is essential that the samples taken are representative of the whole shipment and not just one or two boxes. It is recommended that priority be given to the critical performance parameters of breaking strength and pouch integrity when such testing is undertaken. The risk of statistical Lot failures due to sampling error should be considered when interpreting such tests.

2.7.3 Testing laboratories

Laboratories may be:

- manufacturers’ laboratories
- independent test laboratories
- national regulatory laboratories.

Laboratories that test IUDs for confirmatory or conformity purposes need to have systems in place to ensure reliability of their results. ISO has developed a quality management system specifically for calibration and test laboratories – ISO 17025, by adding specific requirements for these to the requirements ISO 9001 – the foundation standard for quality management systems. Laboratories
that are accredited to ISO 17025 are also ISO 9000 compliant. Test laboratories used for third party testing should be accredited to ISO 17025 and have the testing of IUDs within the scope of their accreditation. Accreditation requires an independent audit to confirm that the laboratory is operating under the requirements of ISO 17025 by an accreditation body and that it performs the tests in its scope as required by the particular separate standards for these tests. The laboratory must conduct regular calibration of its measuring equipment and have an adequate maintenance of the equipment as well as the management system.

There are a number of international mutual recognition agreements among accreditation bodies, which audit each other for quality. The international umbrella body is:

**International Laboratory Accreditation Cooperation (ILAC)**
NATA, 7 Leeds Street Rhodes, NSW Australia.
Telephone: (+61 2) 9736 8222, Telefax: (+61 2) 9745 5311.
Website: http://www.nata.asn.au

When assessing a testing laboratory, the following factors should be considered:

- whether the laboratory is accredited by an internationally recognized body
- whether the laboratory participates in inter-laboratory proficiency trials
- the reputation of the laboratory among large-volume purchasers.

Some countries have medical device regulations that require local testing of imported devices by an approved laboratory. Where a procurement agency has a system involving sampling from the manufacturing site, it may be possible for the agency to have the test results from internationally accredited laboratories accepted in lieu of local testing. Alternatively, if the national regulatory laboratory functions to an accredited standard, it can undertake the conformity testing of IUDs.

### 2.7.4 Lots

A Lot is a homogenous collection of IUDs made at essentially the same time under essentially the same manufacturing conditions using the same lots of raw materials. All IUDs comprising a Lot therefore will:

- be made from the same lots of raw materials and components
- have the same dimensions and meet the same performance requirements
- be manufactured on the same production line with no major interruptions or machine changes

- be sterilized together
- have the same unique identification code or number.

Lot sizes should be selected to meet manufacturers’ and/or customers’ requirements, providing of course that the Lot sizes chosen are compatible with the definition of a Lot. The sampling plans and acceptance criteria specified in this edition of the WHO/UNFPA TCu380A IUD Technical Specification are independent of Lot size. The use of very large Lot sizes (e.g. over 500,000) is not recommended due to the risk of poor within Lot homogeneity and logistics problems that might arise in cases of product recall.

Any significant interruption in production must result in a new Lot being started. Lots must not be comprised of separate interrupted runs.

### 2.7.5 Sampling

#### Determining sample size and acceptance criteria

The quality of each Lot is estimated by testing a randomly selected sample of IUDs from that Lot. The sample sizes given in The Specification (Chapter 3) were determined by reference to ISO 2859-1 Sampling Procedures for Inspection by Attributes. These are the most widely used sampling schemes using attribute criteria to check multiple Lots (that is, accepting or rejecting individual Lots based on a specification requirement such as breaking strength). Most WHO/UNFPA Specifications for reproductive health products specify Acceptable Quality Levels (AQLs) for each of the key quality attributes that the products must comply with. For a number of reasons this approach has not been used in this revision of the WHO/UNFPA TCu380A IUD Technical Specification. ISO 7439:2015, unlike most other international standards for reproductive health products, does not specify AQLs for any attributes. There is a presumption that all the IUDs in a Lot should comply with the requirements of the standard on all attributes. Also, given the nature of the manufacturing processes used for IUDs there should be very little within Lot variability. Once a production line has been set up to produce either the individual components or the fully assembled IUDs it should continue to run in a stable state producing consistent product through to the end of the Lot. For these reasons AQLs are not specified. Instead a sample size is specified for each attribute with the requirement that there shall be no non-conforming IUDs within the sample that is tested.

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1 Single day shift working counts as interruption. Only continuous shifts over one or more 24 hour period would not count as an interrupted run.
An advantage of the scheme is that it keeps the sample sizes down to the minimum required to confirm conformance with the requirements of the Specification. As added protection for the user of the device, a switching rule has been introduced that requires the manufacturer to increase the sample size (tightened inspection) if there is evidence of a deterioration in quality which is indicated by the rejection of two lots out of five or fewer consecutive lots tested. This requirement is based on the principles of the switching rules specified in ISO 2859-1. A manufacturer remains on tightened inspection until evidence of improved quality is demonstrated (by the acceptance of five consecutive lots).

The scheme described above for lot-by-lot and conformance testing depends upon the switch to tightened inspection to ensure that manufacturers operate at the required quality levels. This is not possible for prequalification testing because of the small number of lots sampled. Additionally, a very high level of assurance of conformance with the specification is required for prequalification purposes. Amended sampling requirements are therefore included in Table 3.1 of the Specification for prequalification testing. This table uses larger sample sizes to provide a high level of assurance when testing a small number of lots. Table 3.1 can also be used when testing isolated lots or a small number of lots where the switch to tightened inspection is not possible.

### Sampling method

Sampling for independent testing should be done by the independent laboratory or by an independent sampling organization and not by the manufacturer producing the IUDs. Such sampling is required for prequalification and surveillance testing.

The sampler must verify lot integrity during sampling.

Samples must be:

- taken in accordance with a pre-agreed sampling plan, normally in accordance with Table 3.2 for lot-by-lot testing and Table 3.1 for prequalification testing
- representative of the lot of IUDs
- randomly selected (preferably based on random numbers)
- taken by or under the personal full-time supervision of the sampler.

The sample, once taken, must be sealed and dispatched under the sampler’s supervision.

When taking samples for prequalification testing it may not be possible in all cases to do so according to the above recommendations given the nature of IUD manufacturing processes. Lots are often prepared for specific orders and there may not be a large stock of IUDs available at the time of sampling. It is recommended that purchasers obtain a production plan from the manufacturer and schedule sampling around that production plan in order to assist the sampling laboratory or agent in meeting as many of the above criteria as possible.

At the request of the manufacturer, a duplicate sample may be taken for use in case of disputes. The sampling agency must issue a report on the sampling process, indicating the sampling process, identification of the cases from which the sample was taken, and the total number of cases offered for sampling. The sampler should mark the cases from which samples are taken for buyer reference at receipt.

### 2.7.6 Procedure for independent sampling

Sampling for independent testing should be done by an independent accredited laboratory or an independent sampling organization and not by the manufacturer producing the IUDs. Such sampling is required for prequalification and surveillance testing.

The sampler must verify the integrity of the lot prior to sampling. Samples must be:

- taken in accordance with a pre-agreed sampling procedure
- representative of the lot of IUDs
- randomly selected (preferably based on random numbers)
- taken by, or under, the personal full-time supervision of the sampler.

The sample, once taken, must be sealed and dispatched to the test laboratory under the sampler’s supervision. At the request of the manufacturer or buyer, a duplicate sample may be taken. The sampling agency must issue a report on the sampling process, indicating the sampling process, identification of the cases from which the sample was taken, and the total number of cases offered for sampling. The sampler should mark the cases from which samples are taken for buyer reference at receipt.

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2 Lot integrity is the assurance that all items in the lot are traceable to that lot and were made in a single manufacturing run using the same lots of raw materials.

3 An example of an acceptable sampling procedure for determining the number of exterior shipping cartons from which to draw the sample is the Square Root + 1 Plan. Under this procedure the number of exterior shipping cartons from which to take samples is determined by calculating the square root of the total number of exterior shipping cartons in the lot (e.g., the square root of 100 = 10), plus one additional case. The number of exterior shipping cartons is selected at random, for example, by using appropriate random numbers. The total number of samples required for testing specified by the relevant sampling plan in Table 3.1 or Table 3.2 is then selected equally from among the exterior shipping cartons. Again, selection of the samples from each exterior shipping carton shall be random.
sample may be taken for use in case of disputes and can either be sent to the test laboratory or sealed with tamper-proof tape and left at the manufacturing site. The sampling agency must issue a report on the sampling process, detailing the sampling protocol, identification of the cases from which the individual samples were taken, and the total number of cases offered for sampling. For buyer reference at receipt, the sampler must mark the cases from which samples.

2.7.7 Resolution of disputes arising from prequalification or surveillance testing

It is essential that the procurement contract specify a process for the resolution of any disputes that might arise over contract or product quality issues. There are a number of possible causes of disputes relating to product quality during fulfilment of a contract to supply TCu380A IUDs. Disputes over product acceptance most often arise when independent testing determines that the product is not in conformance with the required specification or standard. It is also possible for a manufacturer to dispute a decision made by the sampling agency regarding product packaging or appearance.

Laboratory testing always uses a sample from the production Lot. In any shipment of IUDs there is always a risk that some Lots will be rejected even though they are in conformance with the specification when tested using the sampling and acceptance criteria given. There are generally three main sources of uncertainty in test results:

- The uncertainty arising due to sampling errors. There is always an intrinsic level of uncertainty in estimating the properties of any population based on testing of a sample due to the sampling alone. This uncertainty decreases as the sample size is increased. The sampling requirements for Lot-by-Lot testing specified in The Specification (Chapter 3) generally provide a 90% probability that an individual Lot that is just within specification will be accepted. Manufacturers can prevent excessive Lot rejections by maintaining process averages for non-conforming products below 1% (below 0.3% for pouch peel strength and integrity). However, manufacturers and purchasing agencies should plan on the assumption that some Lots, possibly up to 5%, might be rejected in the long run.

- The uncertainty of estimate in testing. There is always also an intrinsic level of uncertainty in estimating the property of a device based on the test alone. Laboratories accredited to ISO 17025 using the test methods specified in ISO 7439 should be operating within levels of uncertainty that are smaller than the specified tolerances. Uncertainty due to the test methods is therefore unlikely to be a source of dispute when accredited laboratories are used for testing. This may not be the case if non-accredited laboratories are used.

- Testing or reporting mistakes due to operator error, equipment malfunction, drifts in calibration, transcription errors and other causes. These types of mistakes are, in principle, preventable and should be minimized by application of the quality management system and procedures outlined in ISO 17025. In addition, there is the normal uncertainty associated with measurement. ISO 17025 requires that test and calibration laboratories determine and report the level of uncertainty associated with the test procedures used.

Lots with marginally high levels of non-conforming products still have a significant chance of being accepted in the short term. The switch to the larger sample sizes given in brackets in Table 3.2 of Chapter 3 when there is evidence of poor quality (i.e. two Lot rejections in any consecutive sequence of five or fewer Lots tested) is intended to quickly identify and address any potential quality issues. Once a manufacturer has been forced to switch into using the larger sample sizes, the probability of accepting marginal Lots is considerably reduced, forcing manufacturers to improve product quality or continue to reject excessive numbers of Lots.

As a general rule, when the level of Lot failures exceeds 5% over a large number of Lots, i.e. 50 or more, then doubts can be raised about the quality of the manufacturer’s production. Similarly, if the percentage of Lots rejected exceeds 10% in the short term (e.g. between 5 and 50 Lots), then again doubts can be raised about the quality of the products. With these lot rejection rates, however, manufacturers will be quickly switched into using the larger sample sizes. This will result even higher lot rejection rates, forcing the manufacturer through economic pressure to address the quality issues that are causing the Lot rejections.

Re-testing

Re-testing should be undertaken only when:

- There is considerable evidence that the laboratory has made a mistake.
• There is considerable evidence that the test result is not representative of the population from which the Lot is taken.

Because of the intrinsic uncertainty in any sampling plan for inspection by attributes there can be a significant probability that a rejected Lot will be accepted on re-test even if the Lot is not in conformance with the requirements specified in Chapter 3. This means that in many cases re-testing will lead to conflicting results.

Therefore, re-testing should be undertaken only when there is strong evidence that an error has been made.

Before re-testing is conducted, the following investigative measures should be taken:

• **The following factors should be taken into consideration**
  What is the margin by which the product has failed to comply?
  Is the manufacturer’s history of production for the client a good one?
  What is the nature of the difference between the manufacturer’s and the laboratory’s test results? Are the differences within the margins of uncertainty?

• **Available data should be reviewed and discussed with the independent laboratory.** This should include verification from the independent laboratory on the following:
  Testing was performed as prescribed in the test method applicable to the order concerned.
  Test equipment was in proper working order and in calibration at the time of testing.
  Staff performance was acceptable. This can be evaluated by looking at the relevant tester’s results on other products tested at about the same time.
  The identity of the test samples and that the normal precautions were taken not to damage the samples prior to testing.
  The uncertainty estimates being applied to the measurements.
  The laboratory will keep the non-conforming IUDs until the dispute is resolved.

• **Available data should be reviewed and discussed with the manufacturer.** This should include the following:
  A review of the manufacturing history, in-process test results and final test results for the Lots in question.
  A review with the manufacturer of the verification procedures conducted by the test laboratory.
  A review of any internal investigation performed by the manufacturer following the Lot failure.

When the Lot concerned is part of an on-going order and there is historical or concurrent data on at least 10 Lots, the process average can be estimated. If this process average is within the normal range expected by the manufacturer, a re-test may be allowed.

Where re-testing is done, the second test should be designed to give additional confidence about the result.

The sample sizes and acceptance criteria given in Table 3.1 of Chapter 3.7 were designed to give high levels of consumer protection while maintaining high acceptance probabilities for manufacturers that comply with the Specification. The sample sizes and acceptance criteria given in Table 3.1, Prequalification Testing, are therefore recommended when conducting any retest.

Where possible, the re-tested sample should be taken from the laboratory’s retained sample. If this is insufficient, or if the sample is suspect, a new sample will need to be taken.

In all cases the manufacturer should bear the cost of a re-test, unless it can be demonstrated that it is likely that the laboratory has made a mistake.

### 2.8 Storage

There is extremely good evidence from stability studies conducted by manufacturers and the testing of used TCu380A IUDs removed from patients that the materials used to manufacture the TCu380A IUD have excellent long term ageing properties. All UNFPA prequalified TCu380A IUD manufacturers have also submitted stability data supporting the maximum storage time prior to insertion as part of the prequalification process. Real time studies are always required and accelerated studies may be submitted prior to the real time studies being available, the real time studies being conducted at (30 ± 2) °C and (75 ± 5)% relative humidity to model the most extreme storage conditions (climatic zone IVb, hot humid/tropical). For these reasons IUDs can be expected to have good storage properties even when stored and distributed in countries with hot/humid climates. More information on stability studies can be found in Chapter 5.

The pouch materials are also chosen for their excellent long-term stability but some of the pouch components, such as the bonding layer forming the seal, may not be...
quite so robust. The pouches also have to maintain extremely high levels of integrity throughout the entire storage period from date of manufacture until the “insert before date”. Pouch integrity and peel strength are monitored as part of the stability studies referred to above. The recommended limit of five years for storage applies to IUDs where stability has been determined by accelerated stability studies, seven years is permitted when there is appropriate real-time stability data.

Given the relative robustness of TCu380A IUDs, air-conditioned storage is not necessary, although it could be an advantage in hot climates. IUDs should be stored in a well-ventilated environment, away from direct sunlight and other sources of heat to minimize exposure to high temperatures that could compromise the pouch seals. Similar precautions should be taken during transportation and delivery. IUDs stored outdoors in shipping containers are particularly vulnerable, as the temperatures inside containers can be substantially above ambient temperatures. Storage time in containers should therefore be minimized by effective control of the distribution chain.

The inner boxes (sometimes referred to as secondary packaging or inner cartons) are made from cardboard. Cardboard storage boxes are vulnerable to moisture and should be stored in a dry storeroom away from walls on pallets to protect against rising damp. They should be stored at least 10 cm off the floor, 30 cm away from the walls and stacked no more than 2.4 metres high.

The shipping cartons are made from weather-resistant corrugated fibreboard with an appropriate bursting strength. These cartons are more robust than the inner boxes but nevertheless similar precautions should be used to protect the shipping cartons from moisture.

IUDs should be left in their original cartons and inner boxes until needed for distribution. The cartons should be positioned so that the Lot number, manufacturing date and “insert before date” are visible. The cartons should be identified and their locations recorded to ensure that specific Lots can be located. Lots should be released on a first expiry-first out basis (FEFO).

During storage care should be taken to protect the IUDs from rodents, insects and other animals that could contaminate the pouches or compromise their barrier properties. Damaged or expired IUDs should be kept separately and disposed of in accordance with local procedures for the disposal of damaged medical devices.
Chapter 2 Essential Elements of IUD Quality Assurance
Chapter 3

TCu380A Intrauterine Device Technical Specification
3.1 Introduction

This chapter contains the WHO/UNFPA TCu380A IUD Technical Specification, which is suitable for the bulk procurement of TCu380A IUDs for use in public-sector programmes for family planning. A summary of the technical basis for the WHO/UNFPA Technical Specification is given in Annex I.

The WHO/UNFPA TCu380A IUD Technical Specification primarily covers the buyer’s requirements. Also, included in the Specification is guidance for the manufacturers, which include specifications for the individual components. A Specification is a detailed and unambiguous statement of the requirements and describes the general, design, performance, labelling and packaging requirements for the product and the methods of verification. A Specification is generally attached to the bidding documents and forms part of the supply contract.

The WHO/UNFPA Technical Specification is based on the requirements for copper-bearing IUDs in the International Standard ISO 7439 Copper-bearing contraceptive intrauterine devices - Requirements and tests. This standard specifies the generic requirements for copper-bearing IUDs and the test methods that are used to assess conformance with these requirements. The specific requirements for the TCu380A IUD are based on the Population Council New Drug Application 18-680 (Copper T Model TCu380A). ISO 7439 is referred to generically throughout the Specification; therefore it should be assumed that the most recent edition of the standard should apply.

The Specification is divided into the three following sections:

- **General Requirements** specify the safety of constituent materials and other characteristics, such as shelf life, materials, product and component dimensions, storage, biocompatibility, sterility and method of sterilization. These requirements are normally assessed by material and process validation including testing where appropriate by the manufacturer. Re-validation is required following any significant change to the sourcing of raw materials or changes in the manufacturing processes. The General Requirements detailed in this 2016 edition of the WHO/UNFPA TCu380A IUD Technical Specification should not be changed by the purchaser. Conformance with the General Requirements is verified during prequalification. These characteristics of the product should not change on a Lot-by-Lot basis.

- **Performance Requirements** specify the essential performance attributes of the TCu380A IUDs, established in accordance with ISO 7439 and the Population Council NDA. These must be assessed on a Lot-by-Lot basis by the manufacturer and may be assessed by the purchaser on a Lot-by-Lot basis. These attributes may vary due to the manufacturing process. Performance requirements detailed in this 2016 edition of the WHO/UNFPA TCu380A IUD Technical Specification should not be changed.

- **Packaging and Labelling Requirements** are detailed in this 2016 edition of the WHO/UNFPA TCu380A IUD Technical Specification and should not be changed. Continuous film packaging combined with terminal radiation is preferred as it reduces the risk of tarnishing. Additional labelling may be specified based on programmatic needs.

The WHO/UNFPA Technical Specification is based on:

- The International Standard ISO 7439
- Population Council New Drug Application 18-680 (Copper T Model TCu380A Intrauterine Contraceptive)
- A literature review of the available evidence;
- The recommendations of the WHO/UNFPA IUD Technical Review Committee (November 2006, August 2008 and September 2013)
- Feedback from participants attending the WHO/UNFPA workshops to introduce the TCu380A IUD specification, prequalification and procurement procedures, conducted in Bangkok, Thailand in January 2010 and New Delhi, India in February 2014.

Where appropriate, reference is made to the current edition and corrigenda of the published International Standard, ISO 7439 Copper-bearing contraceptive intrauterine devices - Requirement and tests.

The WHO/UNFPA Technical Specification, if used in conjunction with the WHO/UNFPA Prequalification Programme and procurement procedure, will ensure that a quality assured product is purchased and distributed to the end user.
The TCu380A IUD consists of a T-shaped frame made from low-density polyethylene with barium sulphate added for X-ray opacity (Fig. 1) with a plastic ball at the bottom of the vertical stem to guard against cervical penetration. The IUD has solid copper collars on each of its two horizontal arms. Each of these collars has a surface area of 35 mm². Copper wire with a surface area of 310 mm² is wound tightly around the vertical stem, giving a total surface area of 380 mm² of copper, as indicated in the name of the device. A pigmented polyethylene filament is tied in a knot through a small hole in the ball to provide two equal-length threads as a means to locate and remove the device. The device is packed in an individual pouch and subjected to post packaging sterilization.

Tarnishing is a natural phenomenon for copper and does not affect the performance of the IUD. However, significant tarnishing of copper during storage may not be aesthetically acceptable. The use of continuous film packaging, which is suitable for gamma radiation sterilization, helps to reduce the problem of tarnishing.

In order to insert the device into the uterus an insertion tube is used. The insertion tube keeps the TCu380A IUD correctly positioned within the uterus while the insertion rod is removed. The moveable plastic flange is positioned on the insertion tube to control the depth of insertion and to locate the IUD correctly within the uterus during insertion.

Other devices to assist the process of insertion may also be provided, for example, an arm-folding device, an uterine sound, sterile gloves, sterile swabs etc. When considering design and choice of materials for these components, manufacturers shall take into account the function of the devices, the type and duration of exposure to the body and the effect of sterilization.

Purchasers should assess the functionality, safety and effectiveness of any assist devices including their potential effect on the IUD prior to purchase.

For IUDs specifically manufactured and labeled for postpartum insertion, deviations from the specifications regarding length of string and dimensions of the inserter are permitted if they can be clinically justified.

Copper bearing IUDs are classified under European Medical Device Directive 93/42/EEC (as amended) as Class III medical devices with ancillary medicinal substances (see MEDDEV 2. 1/3 rev 3, Clause B.4.1). The clinical studies detailed in the Technical Basis Paper have all been conducted using TCu380A IUDs complying with the Population Council Specification submitted in NDA 18-680 which requires a minimum copper purity of 99.99%. These studies have demonstrated that the TCu380A IUD based on this Specification is both effective and safe.

### 3.2 General Requirements

The general requirements specified in this section shall not change from Lot to Lot. Conformance with these requirements are assessed during prequalification and also in case of doubts by the purchaser whether the product complies with the Specification. Conformance may need to be assessed if any significant changes are made in the selection/sourcing of materials or the manufacturing procedures. As per prequalification requirements, manufacturers shall inform UNFPA of any changes that impact conformance with general requirements.

#### 3.2.1 Lot definition

**Requirement**

A Lot is a homogeneous collection of IUDs made under essentially identical manufacturing conditions using the same lots of raw materials; low-density polyethylene (LDPE) compound, high-density polyethylene (HDPE) compound, for thread, copper for wire and collars, individual pouches and individual pouch material that are subjected to sterilization in the same sterilization cycle and assigned a unique number before release. Clear Lot identification and recording are required to permit effective product recall in the event of a quality problem with the device.

#### 3.2.2 Date of manufacture

**Date of manufacture requirement**

The date of manufacture of a Lot is the month/year in which the IUDs were sealed in the primary package for terminal sterilization. Sterilization shall be conducted in accordance with Section 3.2.5
### 3.2.3 Materials

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Requirement Details</th>
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</thead>
<tbody>
<tr>
<td><strong>T Frame requirements</strong></td>
<td>The T frame shall be made from LDPE, free of stabilizers, having a minimum tensile strength of 13 MPa (ASTM D638 - ISO 527-2, using a crosshead speed of 50 mm/min and a type 1 specimen bar) and a 2% secant flexural modulus in the range 133.5 MPa to 180.6 MPa (ASTM D790). The LDPE shall be blended with 15% to 25% precipitated barium sulphate USP (United States Pharmacopeia) with a particle size of 95% less than 10 micron. The barium sulphate content of the frame material shall be determined according to the relevant clause of ISO 7439. See also the biocompatibility requirements for compounded polymer below.</td>
</tr>
<tr>
<td><strong>Copper wire requirements</strong></td>
<td>The wire shall be made from oxygen-free electronic (OFE) 99.99% pure copper meeting the National Bureau of Standards designation UNS C10100. There shall be no coating on the wire.</td>
</tr>
<tr>
<td><strong>Copper collars requirements</strong></td>
<td>The copper collars shall be made from half-hard temper, seamless copper tube made from OFE 99.99% pure copper meeting the National Bureau of Standards designation UNS C10100. There should be no coating on the collars.</td>
</tr>
<tr>
<td><strong>Thread requirements</strong></td>
<td>The thread shall be a monofilament made from HDPE, free of stabilizers, with sufficient tensile strength to meet the specified thread breaking force requirement of 9.5 Newton. A material with a minimum tensile strength (ASTM D638 - ISO 527-2) of 28 MPa is recommended. The thread polymer shall be compounded with 0.4% up to 1.0% by weight rutile titanium dioxide USP (EP). See also the biocompatibility requirements for compounded polymer below.</td>
</tr>
<tr>
<td><strong>Insertion tube requirement</strong></td>
<td>The insertion tube shall be made from HDPE food contact grade.</td>
</tr>
<tr>
<td><strong>Insertion rod requirement</strong></td>
<td>The rod shall be made from food contact grade radiation stable acrylonitrile-butadiene-styrene polymer (ABS) or food contact grade radiation-stabilized polypropylene (PP). Optionally, the insertion rod may be pigmented.</td>
</tr>
<tr>
<td><strong>Positioning flange requirements</strong></td>
<td>The flange shall be made from a polymer with adequate radiation stability to permit sterilization without any significant change in properties including flange displacement force. Optionally, the flange may be pigmented.</td>
</tr>
<tr>
<td><strong>Biocompatibility requirement</strong></td>
<td>The compounded T frame polymer (LDPE plus barium sulphate) and compounded thread as an assembly, or separately shall be evaluated for biological safety in accordance with ISO 10993-1 requirements for mucosal membrane contact devices intended for permanent contact. Specifically, the following is required: evaluation for genotoxicity according to ISO 10993-3, evaluation for cytotoxicity according to ISO 10993-5, evaluation for local effects after implantation according to ISO 10993-6, evaluation for irritation and delayed-type hypersensitivity according to ISO 10993-10, evaluation for subacute and subchronic toxicity according to ISO 10993-11.</td>
</tr>
</tbody>
</table>
For a specific material it is only necessary to carry out the assessment of biological safety once. The evaluation shall be repeated if there is a significant change to the materials, for example, if the grade or supplier is changed.

Manufacturers may continue to use DuPont™ 20 LDPE and Phillips 6007 HDPE without conducting the biocompatibility evaluation on the T frame compound with barium sulphate or thread compound with titanium dioxide.

It is required that all biological safety tests in accordance with ISO 10993 parts 1, 3, 5, 6, 10 and 11 be conducted by laboratories accredited for these tests. Detailed requirements are provided in Section 4.6.

**Material procurement and control requirements**

Manufacturers are responsible for ensuring all operations, including those undertaken by subcontractors, such as material storage, compounding of the frame and thread materials, and moulding are done to acceptable standards as specified below. There should be adequate control procedures and documentation to ensure and demonstrate conformance in accordance with ISO 13485.

These procedures should ensure that batches of compounded materials (T frame, thread materials) and moulding and extrusion of the components are not contaminated by any extraneous impurities during processing operations.

Where lubricants are used in moulding and extrusion, the grades shall be “Food Grade” and/or suitable for medical device manufacture.

Materials and components should be stored in a manner in which they are protected from light and high humidity. The storage condition shall ensure conformance with bio-burden levels specified for the product.

If appropriate, the copper components or other components should be cleaned prior to assembly.

Manufacturers shall introduce procedures to monitor and control the degree of tarnish and rough edges on the copper components.

The maximum storage period before retesting of the raw material is required for the frame polymer and the thread is three years from the date of manufacture when stored at temperatures under 30 °C and two years when stored at temperatures between 30 °C and 35 °C.

Provided the breaking force of the frame material exceeds 13 MPa (which may be determined by testing moulded frames) and the breaking force of the thread exceeds 9.5 Newton, then the materials may be used for a further three years when stored at temperatures under 30 °C and 2 years when stored at temperatures between 30°C and 35°C.

Every new Lot of compounded frame material (LDPE plus barium sulphate) and thread material (HDPE plus titanium dioxide) shall be subjected to in vitro cytotoxicity testing in accordance with ISO 10993-5 Biological Evaluation of Medical Devices. Tests for in vitro cytotoxicity, see Section 4.6.

The cytotoxic response shall not be worse than that recorded for the compounded material when originally evaluated for biological safety according to the requirements of ISO 10993-1.

**Material processing requirement**

The recycling of injection moulded reclaim material for the T frame and the thread is NOT permitted.
3.2.4 Shelf life, maximum *in-situ* time and stability

| Stability studies requirement | Shelf-life claims shall be supported by real-time stability data collected in accordance with Chapter 5. Accelerated ageing stability studies may be submitted pending the completion of real-time studies. Guidance on conducting stability studies is given in Chapter 5: Guidance for Stability Studies. |
| 'Insert before date' requirement | The ‘Insert before date’ is the maximum permitted shelf life for storage of the device prior to insertion and is normally five years. By agreement with the purchaser the shelf life may be extended to seven years subject to satisfactory real time stability data being available and reviewed for the full seven years for storage in climatic zone IVB, 30°C/75% Relative Humidity (RH). The stability data shall include package integrity testing substantiating maintenance of sterility. |
| Maximum in-situ time | Based on efficacy and safety evidence the maximum in situ time is 12 years. |

3.2.5 Bioburden control and terminal sterilization

| Sterilization and method requirements | The TCu380A IUD shall be supplied sterile in a sealed primary pack together with the insertion tube, the insertion rod and the positioning flange. Sterilization shall be by radiation according to ISO 11137 series, or by ethylene oxide according to ISO 11135 series and standards normatively referenced therein. Radiation sterilization is preferred, to allow the use of continuous polymer film packaging materials. The sterilization shall be completed within 30 days of sealing the finished device in the pouch. |
| Sterility assurance level requirement | The sterilization assurance level shall be $10^{-6}$. |
| Residual ethylene oxide levels requirement | If ethylene oxide sterilization is used, then residual ethylene oxide levels shall not exceed 10 ppm, and ethylene chlorohydrin levels shall not exceed 20 ppm, on any individual sample when measured using a method that complies with the requirements of ISO 10993-7. Average residual levels across all samples tested shall not exceed 5 ppm for ethylene oxide and 10 ppm for ethylene chlorohydrin. |

3.2.6 Component specifications

| T frame | Length of horizontal arms (total length of both arms): $(32 \pm 0.5)$ mm. Length of vertical stem: $(36 \pm 0.5)$ mm. Diameter of horizontal arm: $(1.6 \pm 0.1)$ mm. Diameter of vertical stem: $(1.5 \pm 0.1)$ mm. Optionally, a hole for anchoring an end of the copper wire may be provided. The maximum diameter of the hole shall be 0.55 mm.  
  • The T piece ball (at the end of vertical stem) shall have a diameter of $(3.0 \pm 0.7)$ mm. The junction between the ball and the vertical stem shall preferably be radiused.  
  • The T piece ball (at the end of vertical stem) shall have a hole of maximum diameter 0.80 mm for securing the thread. The hole may be tapered or dumbbell-shaped. The junctions between the horizontal arms and the vertical stem may be radiused to prevent stress concentrations. If the junction is radiused, the radius shall be between 0.25 and 0.40 mm. |

Manufacturers shall confirm that introducing the radius does not lead to an increase in crush damage at the junction when the T is deformed as it is loaded into the insertion tube. This can be achieved by comparing the strength of radiused and non-radiused T frames after loading in the insertion tube. Microscopic examination should be used alongside strength testing to monitor the extent of any damage.

A drawing of the T frame is included in Annex III.

### Copper wire

The diameter of the wire shall be \((0.255 \pm 0.005)\) mm (30 AWG, 33 ISWG).

### Copper collars

The internal diameter shall be \((1.68 \pm 0.025)\) mm and external diameter \((2.2 \pm 0.025)\) mm. The collars shall be \((5 \pm 0.15)\) mm in length.

The collars shall be deburred, polished and free from sharp edges, for example, by barrel tumbling.

A drawing of the copper collar is included in Annex III, Fig 2.

### Thread

The thread diameter shall be \((0.25 \pm 0.05)\) mm.

### Insertion tube

The length of the insertion tube shall be \((206 \pm 2)\) mm.

The internal diameter of the insertion tube shall be \((3.7+0.2/-0.1)\) mm. This should be determined using a plug gauge.

The outside diameter of the insertion tube shall be \((4.4+0.2/-0.1)\) mm.

### Insertion rod

The length of the insertion rod shall be \((190 \pm 5)\) mm from handle brace to tip.

The insertion rod shall be a snug fit but slide smoothly within the insertion tube and shall not trap the thread.

It is recommended that the rod have a thickened section, spline or ridge, to help retain the rod within the insertion tube.

The diameter of the insertion rod at tip shall be \((2.6 \pm 0.2)\) mm. The rod diameter should be equal to or less than the tip diameter.

### Testing

Preferably the dimensions should be determined using non-contact methods such as a projection microscope. Appropriate gauges and/or callipers may be used as an alternative.

The internal diameter of insertion tube is assessed by using appropriate plug gauges.

### 3.2.7 Flexibility test

#### Requirement

When tested according to the test method given in Section 3.6.2 the deflection of the horizontal arm from the horizontal measured at the point on the arm where the load is applied shall be greater than 4.0 mm. A suitable test jig may be used to clamp the T frame and amplify the deflection of the arm, in which case the deflection on the scale shall be greater than that equivalent to a deflection of 4 mm at the point on the arm where the load is applied.

This test must be performed on frames prior to assembly. Therefore, verification of conformance with this requirement shall be confirmed at prequalification and re-qualification.

#### Testing

According to the test method given in Section 3.6.2.
### 3.3 Finished Product Requirements

These requirements are assessed on finished products during prequalification and/or surveillance testing. They may also be used for assessing product on a Lot-by-Lot basis and when doing in-country testing. Testing should be based on the sampling requirements given in Chapter 3.7.

### 3.3 Finished product requirements (to be evaluated during prequalification and surveillance and testing)

#### 3.3.1 T frame

<table>
<thead>
<tr>
<th>Requirements</th>
<th>All IUDs measured in a test sample shall fall within these ranges:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Length of horizontal arms (total length of both arms): ((32 +1.0/- 0.5) \text{ mm.})</td>
</tr>
<tr>
<td></td>
<td>• Length of vertical stem: ((36 + 1.0/- 0.5) \text{ mm.})</td>
</tr>
<tr>
<td></td>
<td>• Diameter of horizontal arm: ((1.6 \pm 0.1) \text{ mm.}) The measurement should be taken between the collars.</td>
</tr>
<tr>
<td></td>
<td>• Diameter of vertical stem where it is not covered by copper wire: ((1.5 \pm 0.1) \text{ mm.})</td>
</tr>
<tr>
<td></td>
<td>• The vertical stem shall terminate in a ball. The T piece ball (at the end of vertical stem) shall have a diameter of ((3.0 \pm 0.7) \text{ mm.}) The junction between the ball and the vertical stem shall preferably be radiused.</td>
</tr>
<tr>
<td></td>
<td>• The T piece ball (at the end of vertical stem) shall have a hole for securing the thread.</td>
</tr>
</tbody>
</table>

A drawing of the T frame is included in Annex III.

| Testing | Preferably the dimensions should be determined using non-contact methods such as a projection microscope. Appropriate gauges and/or callipers may be used as an alternative. The diameter of the horizontal arm shall be measured between the collars. |

#### 3.3.2 Thread

| Requirements | The thread shall be knotted to form two tails of approximately equal length. The length of each tail shall be not less than 105 mm and not greater than 125 mm. |

| Testing | The length of the tails shall be measured using a calibrated rule from the base of the T piece ball. |

#### 3.3.3 Copper collar

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Collar position: ((5.4 \pm 0.4) \text{ mm from the ends of the T horizontal arm. The measurement shall be taken from the ends of the arms.})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Collar weight shall be ((68.7 \pm 3.0) \text{ mg.})</td>
</tr>
<tr>
<td></td>
<td>A drawing of the copper collars is included in Annex III.</td>
</tr>
</tbody>
</table>

| Testing | Preferably the dimensions should be determined using non-contact methods such as a projection microscope. Appropriate gauges and/or callipers may be used as an alternative. |

#### 3.3.4 Copper surface area

<table>
<thead>
<tr>
<th>Requirements</th>
<th>The nominal surface area shall be 380 mm(^2) with a tolerance of (\pm 10%) (tolerance specified in ISO 7439). Provided the copper collar and copper wire weights are within the specified limits below, the surface area will comply with the requirements of this Specification and ISO 7439 tolerances.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Collar weight shall be ((68.7 \pm 3.0) \text{ mg.})</td>
</tr>
<tr>
<td></td>
<td>Wire weight shall be ((176 \pm 11) \text{ mg.})</td>
</tr>
</tbody>
</table>

| Testing | The weight of the wire and collars shall be determined using a balance after careful removal from the frame. |
3.3.5 Copper wire winding

Requirement  
The wire shall be wound so that it is in contact with the frame and is uniform. The proximal and distal ends of the wire must lie smoothly on the T surface and not protrude beyond the wire profile in order to prevent any chance abrasion of uterine tissue during insertion or in situ.

The length of wire protruding from the anchoring hole ("the tag") shall not exceed 10 mm. It shall be bent to point down the vertical stem and not interfere with the position of the arms when the IUD is placed in the insertion device.

Both single- and double-wound configurations are acceptable.

Testing  
By visual inspection.

3.3.6 Insertion tube

Requirement  
The length of the insertion tube shall be (206 ± 2) mm.

The internal diameter of the insertion tube shall be (3.7+ 0.2/- 0.1) mm. This should be determined using a plug gauge.

The outside diameter of the insertion tube shall be (4.4 + 0.2/- 0.1) mm.

Testing  
The internal diameter is assessed by using an appropriate size plug gauge.

The measurement of outside diameter shall be taken at three locations; two within 2-3 cm from either end of the tube, and one within the approximate mid-point.

Non-contact methods are preferred for the outside diameter.

3.3.7 Insertion rod

Requirement  
The length of the insertion rod shall be (190 ± 5) mm from handle brace to tip.

The insertion rod shall be a snug fit but slide smoothly within the insertion tube and shall not trap the thread.

It is recommended that the rod have a thickened section, spline or ridge, to help retain the rod within the insertion tube.

The diameter of the insertion rod at tip shall be (2.6 ± 0.2) mm. The rod diameter should be equal to or less than the tip diameter.

Testing  
Dimensions shall be determined using appropriate calibrated rules, gauges and/or calipers or non-contact techniques.

Assess the fit of insertion rod by inspection.

3.3.8 Insertion tube flange

Requirement  
The shape and dimensions of the central hole shall be such that the specified flange displacement force specification is met.

Testing  
By visual inspection.
### 3.4 Performance Requirements

When tested according to the relevant clause of ISO 7439 or, if appropriate the specified test method in this document, the performance requirements of the finished product after sterilization shall comply with the requirements specified below. Verification of performance requirements shall be done as part of prequalification and/or surveillance testing. Testing should be based on the sampling requirements given in Chapter 3.7.

#### 3.4 Performance requirements (to be evaluated during prequalification and/or surveillance testing)

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.4.1 Breaking strength</strong></td>
<td>According to the relevant clause ISO 7439. Further information about testing for breaking force is given in Section 3.6.1.</td>
</tr>
<tr>
<td><strong>3.4.2 Copper collar retention force</strong></td>
<td>According to the test method given in Section 3.6.3.</td>
</tr>
<tr>
<td><strong>3.4.3 Memory</strong></td>
<td>According to ISO 7439.</td>
</tr>
<tr>
<td><strong>3.4.4 Thread knot</strong></td>
<td>By visual inspection.</td>
</tr>
<tr>
<td><strong>3.4.5 Insertion rod</strong></td>
<td>By inspection.</td>
</tr>
<tr>
<td><strong>3.4.6 Flange displacement force</strong></td>
<td>According to the method given in Section 3.6.4.</td>
</tr>
<tr>
<td><strong>3.4.7 Product defects</strong></td>
<td></td>
</tr>
</tbody>
</table>

#### Defects:

Manufacturers and testing laboratories should maintain a list of these defects, with clear definitions and diagrams or photographs to assist both in the assessment of workmanship and in the resolution of any disputes. Below are listed the most common types of defects encountered.

- Insecure thread knot
- Defective flange displacement force
- Defective insertion rod
- Defective copper collar retention force
- Defective memory
- Defective breaking strength

Finished IUDs should be inspected visually for evidence of visible defects. The severity of defects may vary depending upon the level of impact they may have on the safety, effectiveness and acceptability of the product. The number of pieces to be inspected are given in Section 3.7.3. All IUDs comprising the sample shall comply with the requirements for visible defects listed below.
Assessed by visual examination, not measurement:
- severe tarnishing of the copper collars or wire
- slight tarnishing (acceptable with the agreement of the purchaser)
- missing components and/or empty pouch
- flash on the mould lines of the T frame
- sharp protruding edges and/or burrs
- unsecured or missing thread (including loose or unsecure knot)
- incomplete/deformed ball
- deformed or loose collars
- improperly sealed pouches
- embedded and/or surface foreign particles on any component within the sealed pouch
- transfer of any printing onto the device
- insertion rod bent or distorted
  (acceptable at the discretion of the purchaser if still usable)
- discoloration of insertion tube or rod

**Testing**

By inspection of visible defects.

### 3.5 Packaging, Labelling and Information Requirements

**3.5.1 Device**

**Markings requirements**

The insertion tube may optionally be printed with depth gauge markings. Manufacturers may mark the frame of the device for identification purposes given that it does not affect the function and safety of the product.

**Testing**

By inspection of the product.

**3.5.2 Individual pouch and insert (primary packaging)**

**Definition**

Individual pouches, sometimes referred to primary or individual packaging, are the protective packaging in which the products are provided. The IUDs are sealed into the individual pouches prior to sterilization.

**Packaging requirements**

Each TCu380A IUD shall be packed in an individual pouch. All pouches shall be sealed.

Packaging materials shall comply with ISO 11607 Part 1.

If an insert is used, it should not affect the safety and performance of the device and not be affected by the method of sterilisation. The total bioburden of the insert and the device shall be controlled prior to sterilisation in accordance with the validated sterilisation protocol.

**Testing**

Sealed pouch integrity shall be tested according to ASTM D 3078 (standard test method for determination of leaks in flexible packaging by bubble emission).

If permeable packaging material is used, sealed pouch integrity shall be tested by ASTM F 1929 (standard test method for detecting seal leaks in porous medical packaging by dye penetration) using Method B (edge dip method). This method shall only be used for permeable packing materials.

**Sealed pouch strength requirements**

The peel force shall be not less than 4.4 N and not greater than 19 N for a test sample width of 25.4 mm.

**Testing**

Testing shall be conducted according to ASTM F 88 (standard test method for seal strength of flexible barrier materials). Details regarding the test method are included in Section 3.6.5.

**Labelling requirements**

The information shall be printed on the primary container or on an insert that is clearly visible through the primary container.
The following information, as a minimum, should be included on the individual pouch or on an insert in the individual pouch. All labelling shall be clearly legible.

- LOT identification number.
- Month and year of manufacture in language(s) to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number or abbreviation as agreed with the buyer.
- ‘Insert before date’ (previously referred to latest insertion date [LID] or expiry date). The ‘insert before date’ is the date after which the product cannot be inserted in utero. The ‘insert before date’ shall be printed in language(s) to be specified by the purchaser and shall be based on the maximum product shelf life from the date of sterilization. The year will be written as a four-digit number and the month as a two-digit number. If manufacturers choose to include the term ‘expiry date’ on packaging this must be in brackets below the ‘insert before date’ and the meaning of ‘expiry date’ must be defined.
- The maximum lifetime in situ. The maximum length of time that the device can remain in utero shall be printed on the primary container. This period shall not exceed 12 years from the date of insertion.
- Manufacturer’s name and registered address.
- The word ‘STERILE’ and the methods of sterilization.
- The words ‘For single use only’ or equivalent.
- Phrase, ‘should be administered by a skilled healthcare provider’.
- Indication that the device is a TCu380A.

**Testing**

By inspection of manufacturers documentation during inspection and visual inspection during prequalification testing and surveillance testing.

### 3.5.3 Consumer packaging

**Definition**

A consumer package contains an individual pouch and will commonly contain branding information.

**Requirements**

The WHO/UNFPA TCu380A IUD Technical Specification contains no requirements for consumer packaging. If consumer packaging is required, then the full design of consumer pack should be specified in accordance with the requirements of the programme.

**Testing**

If consumer packaging is specified, then the consumer packs should be visually inspected for conformance.

### 3.5.4 Inner boxes

**Definition**

Inner boxes, sometimes referred to as secondary packaging or inner cartons, contain specified quantities of IUDs in their individual pouches.

**Packaging requirements**

The individual pouches shall be packed in inner boxes. The inner boxes shall be constructed of cardboard. A suitable moisture-resistant barrier on its inner or outer surfaces may be specified by the purchaser. The boxes shall be of sufficient strength and rigidity to retain their shape through every stage of the supply chain.

**Labelling requirements**

The inner boxes will be marked in a legible manner to describe the contents and to facilitate identification in case of subsequent query. The following information as a minimum shall be included on the inner box. All labelling shall be clearly legible.

- LOT identification number.
- Month and year of manufacture in language(s) to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number or abbreviation as agreed with the purchaser.
3.5.5 Exterior shipping cartons

**Definition**
Exterior shipping cartons, sometime referred to as outer boxes/cartons, are the outer containers in which individual pouches within inner boxes are shipped.

**Packaging requirements**
The inner boxes shall be packed into plastic or other waterproof lining bags, which will be placed in three-wall cartons made from weather-resistant corrugated fibreboard of sufficient strength to avoid products being damaged during shipment.

The carton flaps shall be secured with water-resistant adhesive or with appropriate water resistant tape.

Alternatively, the cartons may be secured by plastic strapping at not less than two positions.

Alternatively, wire-bound, cleated plywood or nailed wood boxes are acceptable when lined with a waterproof barrier material.

The barrier material must be sealed at the edges with waterproof tape or adhesive, and there must be no sharp protrusions inside the boxes.

**Labelling requirements**
The exterior shipping cartons will be marked in a legible manner to describe the contents and to facilitate identification in case of subsequent query.

The following information as a minimum shall be included on the exterior shipping carton. All labelling shall be clearly legible.

- Lot identification number.
- Manufacturer name and registered address.
- Month and year of manufacture in language(s) to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number or abbreviation as agreed with the buyer.
- Number of pieces contained in the shipping carton.
• ‘Insert before date’ in language(s) to be specified by the purchaser. The year will be written as a four-digit number and the month as a two-digit number.
• Instructions for shipping and handling including the phrase, ‘Store in a dry place away from direct sunlight and sources of heat’. There is no need to specify a maximum storage temperature on the packaging.
• Description of the contents as ‘medical devices’
• Any specific labelling required by local regulations and/or regulation(s) in country into which the product is being shipped.
• Other information as specified by the purchaser.

**Testing**
By inspection of manufacturers documentation during inspection and visual inspection during prequalification testing and surveillance testing.

### 3.5.6 Packaging and labelling visible defects

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual pouch and insert</td>
<td>Individual pouches should be inspected visually for evidence of visible defects. Common individual pouch and insert defects include:  - discoloured film and labels;  - missing or incorrect labelling information as specified in Clause 5.2;  - pouch with open or damaged seals; and  - unclear and not readily legible printing on individual pouch and insert.</td>
</tr>
<tr>
<td>Consumer packaging</td>
<td>Not specified</td>
</tr>
<tr>
<td>Inner boxes</td>
<td>Inner boxes should be inspected visually for evidence of visible defects. Common inner box defects include:  - damaged boxes that may affect the integrity, quality or distribution of the IUDs inside;  - empty or partially filled inner boxes;  - missing or incorrect labelling information as specified in Clause 5.4; and  - unclear and not readily legible printing on inner box.</td>
</tr>
<tr>
<td>Exterior shipping cartons</td>
<td>Exterior shipping cartons should be inspected visually for evidence of visible defects. Common exterior shipping carton defects include:  - damaged shipping cartons that may affect the integrity, quality or distribution of the IUDs inside;  - empty or partially filled exterior shipping cartons;  - missing or incorrect labelling information as specified in Clause 5.5; and  - unclear and not readily legible printing on exterior shipping cartons.</td>
</tr>
</tbody>
</table>
3.6 Laboratory Test Methods

Further details of the test procedure are given in this section. These include modification to the test methods given in ISO 7439 or test methods that are specific to the TCu380A IUD.

All testing shall be performed at a temperature of (23 ± 2) °C.

3.6.1 Breaking strength

The IUD shall be tested according to ISO 7439 with the arms of the T frame bent upwards and clamped parallel to each other at a distance of (8 ± 2) mm apart with a single tail thread clamped at a distance of 5 mm from the point of attachment to the IUD. The arms of the T frame shall be clamped by the copper collars only. Conditioning, as specified in relevant clause of ISO 7439 needs to be carried out only in the case of disputes.

An example of a suitable clamp for holding the device is shown below (see Photos 1 and 2).

3.6.2 Flexibility test

This test is used by the manufacturer to confirm the flexibility of the frame. A 20 g weight is applied to one of the horizontal arms of the T frame for a period of 30 seconds at a distance 12 mm from the vertical arm. The deflection of the arm from the horizontal position is measured at the point on the arm where the load is applied.

A suitable test jig may be used to clamp the T frame and measure the amplitude of the deflection. A pivoted needle or lever may be used to amplify the deflection of the horizontal arm. A photograph of a suitable test jig is shown in Photo 3: Flexibility apparatus. Technical drawings for this measurement equipment can be requested from UNFPA. If such a test jig is used, the T frame arm deflection may be converted into a scale reading using the appropriate amplification factor for the jig.

The test shall be carried out at a temperature of (23 ± 2) °C on frames that are at least 96 hours old from the time of moulding. Before testing, the T frames shall be stored for at least 6 hours at the test temperature.

3.6.3 Copper collar retention force

Testing shall be conducted using a suitable measuring device, such as a tensile testing machine, that can measure the displacement force at a separation speed of (200 ± 20) mm/min.

During the copper collar retention force test, the device shall be clamped by the collar on one of the arms, using a suitable jig if necessary, and the opposing arm shall be gripped in the opposite clamp. The force applied to the clamped collar shall not be sufficient to crush the collar and cause it to tighten onto the arm. This can be achieved, for example, by gripping the collar with a clamp having a groove milled with a 1.59 mm (1/16 inch) ball end mill to a
depth of 1.38 mm, or about 65% of the collar diameter, to prevent crushing the collar.

Alternatively one collar may be clamped in one jaw with sufficient force to ensure that it is partially crushed and tightened onto the arm so that there is no slippage during the test. The other collar shall be clamped lightly in the opposing jaw so that it is not crushed and tightened onto the arm. This can be achieved, for example, by using a clamp having a groove milled with a 1.59 mm (1/16 inch) ball end mill to a depth of 1.38 mm, or about 65% of the collar diameter, to prevent crushing the collar.

A picture of a suitable clamp is shown in below:

3.6.4 Flange displacement force
Testing shall be conducted using suitable measuring equipment, such as a tensile testing machine, that can measure the displacement force at a displacement speed of (200 ± 20) mm/min. A suitable test rig will be required to clamp the tube and apply a displacement force to the flange. An appropriate load cell should be used such as a 50 N or 10 N load cell.

The displacement force should be assessed after any initial ‘set’ is overcome. Record the highest force measured once the flange is moving.

To remove set, the flange should be moved over a distance of 1 cm along the tube in the same direction as it will be moved during the test. This can be done manually or by using a suitable jig. The displacement force shall be measured immediately after removal of the set.

3.6.5 Sealed pouch peel strength requirements
Carefully open at the end of the individual pouch as directed on the insert. This end normally has an angled shaped seal. Limit the extent of opening so it is just sufficient to be able to withdraw the pouch contents. Carefully remove the contents of the pouch. Cut two strip samples using a 25.4 mm wide die. If a 25.4 mm wide die is not available, a die within the range of 20-40 mm may be used and the minimum and maximum peel strength requirements as specified in Clause 5.2 shall be adjusted on a pro rata basis. The first sample shall be cut across at the approximate mid-point of the individual pouch. The second sample shall be cut parallel to the long axis of the individual package incorporating the intact end seal at the opposite end to where the pouch has been opened.

For the sample cut across the individual pouch, one of the sealed ends shall be cut off leaving a v-shaped sample as indicated in Photo 7 of *ASTM F 88 ‘fin seal’*. The seal strength of the ‘end seal’ and ‘side seal’ samples shall then be determined according to the following methods:

- if the packaging is made from two equally flexible materials, Technique B of *ASTM F 88* shall be used (sample supported at an angle of 90° by hand); and
- if a rigid material is used as part of the pack, for example, a moulded tray, then Technique C of *ASTM F 88* shall be used (sample supported at an angle of 180°).
3.6.6 Biocompatibility evaluation

Biocompatibility evaluation shall be conducted according to the methods described in the relevant part of ISO 10993. When testing is necessary, it is recommended that extracts are used to assess biocompatibility. Suitable extraction media may include culture medium with or without serum, serum and saline depending upon the specific test that is being conducted. Extraction shall be conducted according to ISO 10993-12. The recommended extraction conditions are (72 ± 2) hours at (50 ± 2) °C. The recommended ratio of sample to extraction medium is 0.2 g per 1 ml. It is permissible to test either the compounded polymers or the moulded frame and thread. If the finished products are used for this testing, the copper wire and collars should be removed to prevent the risk of false positive results.

Some regulatory authorities may require additional testing or certain tests to also be done using non-polar extraction media such as pharmacopeial grades of cottonseed or sesame oil. Specific tests requirements should be confirmed locally before undertaking any testing.

For cytotoxicity testing it is recommended that a quantitative test is used. A suitable test can be selected from following annexes of ISO 10993-5:

Annex A: Neutral red uptake (NRU) cytotoxicity test.
Annex B: Colony formation cytotoxicity test.
Annex C: MTT cytotoxicity test.
Annex D: XTT cytotoxicity test.

Results should be reported as IC50 or Viab % values as appropriate.

Laboratories with accreditation for these tests shall be used for all biocompatibility testing. The results shall be interpreted by a suitably qualified toxicologist or other suitable expert.
3.7 Sample Sizes and Acceptance Criteria for Testing

3.7.1 Sample sizes and acceptance criteria for WHO/UNFPA prequalification testing

Sample sizes and acceptance criteria for prequalification testing are given in Table 3.1. These sample sizes are intended to provide a very high level of confidence that the product conforms to The Specification requirements. They also take account of difficulties often encountered by inspectors and sampling agencies when trying to take samples for prequalification testing.

3.7.2 Samples sizes and acceptance criteria for continuing series of Lots

Sample sizes and acceptance criteria for continuing series of Lots are given in Table 3.2. These sample sizes are applicable when a series of at least 5 Lots is being assessed. They can be used, for example, by purchasers who wish to conduct pre-shipment or confirmatory testing. They are also recommended when in-country testing is carried out and can also be used by manufacturers for assessing the conformance of production Lots.

For any requirement there shall be no non-conforming units in the sample tested. If at any time two out of five (or fewer than five) consecutive Lots are found to be non-conforming on any specific requirement then the number of samples used to assess the conformity for future Lots shall be increased to the number given in brackets for that specific requirement (tightened inspection). The sample sizes given in the brackets shall continue to be used until five consecutive Lots have been found to be acceptable for that requirement (i.e. change from tightened inspection to normal inspection). The sample sizes for continuing series of Lots specified in Table 3.2 apply only when five or more Lots are being assessed.

In addition to using the sample sizes and acceptance criteria given in Table 3.2 for assessing production Lots, it is recommended that manufacturers adopt statistical process control procedures, such as the use of control charts, to ensure that their products conform to The Specification. It is also strongly recommended that manufacturers conduct periodic process capability studies to confirm that their processes are operating within acceptable tolerances.

3.7.3 Sample sizes and acceptance criteria for isolated Lots

Sample sizes and acceptance criteria for assessing the conformity of fewer than 5 Lots are given in Table 3.2. These sample sizes are recommended for surveillance testing where only a limited number of Lots are assessed. They can also be used for confirmatory and/or in country testing on small shipments and for testing retained or returned samples from Lots following complaints and/or in use failures. The sample sizes have been increased to provide a higher level of confidence in deciding whether or not an individual Lot conforms to The Specification requirements.

A total sample of 600 IUD pieces taken from between 1 to 20 Lots, depending upon the production plan of the manufacturer, is required for testing. This includes a small contingency (20) in case there are problems with any of the samples or tests. Please note the total sample size for prequalification is 600 pieces despite the number of Lots the sample is taken from.

UNFPA will determine the sampling plan following review of production plans supplied by the manufacturer.

The IUDs contained in the packages subjected to the package seal integrity and peel strength tests can be used for testing. All dimensional measurements can be conducted on the same IUDs samples.
## Table 3.1: Samples sizes and acceptance criteria for WHO/UNFPA pre-qualification testing of the TCu380A IUD

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Prequalification</th>
<th>Reference Clause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample Size From all Lots</td>
<td>Max Permitted Nonconforming Units per Sample</td>
</tr>
<tr>
<td>Frame Dimensions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length horizontal arms</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Length vertical stem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of horizontal arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of vertical stem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T piece ball diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thread Length</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Copper Collars</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Position</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper Collar Retention force</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper wire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper wire weight</td>
<td>125</td>
<td>2</td>
</tr>
<tr>
<td>Copper wire winding</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Insertion Tube</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insertion tube dimensions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Internal diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>External diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insertion rod dimensions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Diameter at tip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit in insertion tube</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breaking strength</td>
<td>200</td>
<td>5</td>
</tr>
<tr>
<td>Memory</td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td>Flange displacement force</td>
<td>50</td>
<td>2</td>
</tr>
</tbody>
</table>
### Packaging

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Sample Size From all Lots</th>
<th>Max Permitted Nonconforming Units per Sample</th>
<th>Reference Clause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sealed pouch integrity (date of spec publication- Dec 31, 2016)</td>
<td>500</td>
<td>7</td>
<td>3.5.2</td>
</tr>
<tr>
<td>Sealed pouch integrity (Jan 1, 2017 to Dec 31, 2017)</td>
<td>500</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sealed pouch integrity (Jan 1, 2018 onward)</td>
<td>500</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Package pouch peel strength

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Sample Size From all Lots</th>
<th>Max Permitted Nonconforming Units per Sample</th>
<th>Reference Clause</th>
</tr>
</thead>
<tbody>
<tr>
<td>End seal</td>
<td>80</td>
<td>2</td>
<td>3.5.2</td>
</tr>
<tr>
<td>Side seal</td>
<td>80</td>
<td>2</td>
<td>3.5.2</td>
</tr>
</tbody>
</table>

### Product Defects

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Sample Size From all Lots</th>
<th>Max Permitted Nonconforming Units per Sample</th>
<th>Reference Clause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defects (including knot security)</td>
<td>125</td>
<td>3</td>
<td>3.4.7</td>
</tr>
</tbody>
</table>

### Table 3.2: Sample sizes and acceptance criteria for testing of continuing series of Lots and isolated Lots of TCu380A IUDs.

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Sample Size for Normal (Tightened) Inspection</th>
<th>Max Permitted Nonconforming Units per Sample</th>
<th>Reference Clause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length horizontal arms</td>
<td>8 (13)</td>
<td>0</td>
<td>32 1</td>
</tr>
<tr>
<td>Length vertical stem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of horizontal arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of vertical stem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T piece ball diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thread Length</td>
<td>8 (13)</td>
<td>0</td>
<td>32 1</td>
</tr>
<tr>
<td>Requirement</td>
<td>Continuing series of Lots</td>
<td>Isolated Lots (Surveillance Testing)</td>
<td>Reference Clause</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------</td>
<td>--------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td></td>
<td>Sample Size for Normal (Tightened) Inspection</td>
<td>Max Permitted Nonconforming Units per Sample</td>
<td>Sample Size (pieces)</td>
</tr>
<tr>
<td>Copper Collars</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Position</td>
<td>8 (13)</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper Collar Retention force</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper wire weight</td>
<td>20 (32)</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>Copper wire winding</td>
<td>8 (13)</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Insertion Tube</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>8(13)</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Internal diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insertion rod dimensions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>8(13)</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Diameter at tip</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit in insertion tube</td>
<td>8(13)</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Breaking strength</td>
<td>13 (20)</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Memory</td>
<td>8(13)</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Flange displacement force</td>
<td>8(13)</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Packaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sealed pouch integrity (date of publication- Dec 31, 2016)</td>
<td>20(32)</td>
<td>0</td>
<td>125</td>
</tr>
<tr>
<td>Sealed pouch integrity (Jan 1, 2017 - Dec 31, 2017)</td>
<td>50 (80)</td>
<td>0</td>
<td>125</td>
</tr>
<tr>
<td>Sealed pouch integrity (Jan 1, 2018 onward)</td>
<td>125(200)</td>
<td>0</td>
<td>125</td>
</tr>
</tbody>
</table>
## Chapter 3  TCu380A Intrauterine Device Technical Specification

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Continuing series of Lots</th>
<th>Isolated Lots (Surveillance Testing)</th>
<th>Reference Clause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample Size</td>
<td>Max Permitted Nonconforming Units</td>
<td></td>
</tr>
<tr>
<td></td>
<td>for Normal</td>
<td>per Sample</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Tightened) Inspection</td>
<td>(pieces)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max Permitted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonconforming Units</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>per Sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sealed pouch peel strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End seal</td>
<td>13(20)</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Side seal</td>
<td>13(20)</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Product Defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defects (including knot security)</td>
<td>13(20)</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Individual pouch</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Inner box(if consignent includes less than 13 inner boxes, inspect all boxes)</td>
<td>13(20)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Exterior shipping carton (if consignent includes less than 13 exterior shipping cartons, inspect all boxes)</td>
<td>13(20)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Product Defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defects (including knot security)</td>
<td>13(20)</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Individual pouch</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Inner box(if consignent includes less than 13 inner boxes, inspect all boxes)</td>
<td>13(20)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Exterior shipping carton (if consignent includes less than 13 exterior shipping cartons, inspect all boxes)</td>
<td>13(20)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Product Defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defects (including knot security)</td>
<td>13(20)</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Individual pouch</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Inner box(if consignent includes less than 13 inner boxes, inspect all boxes)</td>
<td>13(20)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Exterior shipping carton (if consignent includes less than 13 exterior shipping cartons, inspect all boxes)</td>
<td>13(20)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Chapter 4

Guidance for Bioburden Control and Terminal Sterilization
4.1 Introduction and WHO/UNFPA Requirement

The sterility assurance level (SAL) required in this Technical Specification and for WHO/UNFPA prequalification for terminally sterilized IUDs is $1 \times 10^{-6}$. Sterility testing alone following terminal sterilization cannot provide adequate confirmation of sterility at this assurance level even when a large sample size is tested. The risks of the testing leading to false positives further rule this out as a single viable approach to verification of the achieved SAL.

Sterility Assurance at this level can be achieved by a combination of the following:

- Validation and routine control of the sterilization process
- Validation, control and monitoring of the bioburden on the product.

This is the approach adopted by the sterilization standards that are required and outlined in this WHO/UNFPA TCu380A IUD Technical Specification and Prequalification Guidance document. All pre-qualified IUD manufacturers are required to demonstrate conformance with the ISO 11737-1 requirements for establishment of acceptable limits for bioburden on a medical device based on historical data. The following text provides guidance on achieving the recommended SAL and demonstrating conformance with ISO 11737-1.

4.2 Sterility Assurance Level

Sterility assurance level (SAL) is the probability of a single unit being non-sterile after it has been subjected to sterilization. The SAL shall be at least $1 \times 10^{-6}$.

4.3 Normative Standards for Sterility Assurance

The following standards and guidance are recommended. The manufacturer should ensure conformance with the latest published version of the applicable standards that apply to their sterilization process and bioburden assessment test methods. The latest edition of the standards shall be used by manufacturers.

ISO 13485 Medical devices - Quality management systems - Requirements for regulatory purposes.

ISO 17665 Sterilization of health care products - General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process.


ISO 11137-2 Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process.


ISO 14937 Sterilization of medical devices - General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process.

ISO 11135 Medical devices - Validation and routine control of ethylene oxide sterilization.


4.4 Sterilizer Process Validation

Prequalified manufacturers of IUDs are required to use terminal sterilization facilities that are certified to ISO 13485 and in conformance with the applicable sterilization standards appropriate for the sterilization of IUDs, such as ISO 11137 for Radiation Sterilization or ISO 11135 for Ethylene Oxide sterilization. Radiation is often considered the preferred sterilization method for IUDs, despite the potential adverse effects radiation may have on some materials. Radiation permits the use of impermeable packaging pouches made of a film-film layer combination that can reduce the risk of compromising sterility compared to the
use of gas permeable pouches made of a film – gas permeable synthetic layer combinations that are required for ethylene oxide (or other gas) terminal sterilization methods.

The principles of sterilizer process validation and control are similar for radiation, ethylene oxide and other sterilization methods but and this guidance focuses on radiation sterilization for the above mentioned reasons. In most cases radiation sterilization is subcontracted to a service provider and in such cases it is important to note that the IUD manufacturer is responsible for a high degree of control over the service provider.

The terminal radiation sterilization standards provide at least two methods of establishing the applicable radiation dose. In the first method the sterilization dose is set based on knowledge of the number and/or resistance of the bioburden (microorganisms) on the product to radiation. In the second method the dose is fixed at a defined level (such as 25 kGy or 15 kGy) and the primary manufacturer has to substantiate that the selected sterilization dose is capable of achieving the specified requirements for sterility.

Of the two methods, using a fixed dose (such as 25 kGy) is widely used for medical devices and is preferred for the terminal sterilization of TCu380A IUDs. This dose is widely used within the industry and has been established over many years of use as being safe and effective. If the dose is changed then validation by the methods specified in the appropriate standards would be required to confirm that the sterility, safety and effectiveness of the IUDs are not compromised. A pre-qualified TCu380A IUD manufacturer would also have to obtain the prior agreement from UNFPA for the change by submitting a validation protocol and a report supporting the change for review by an appropriate technical expert.

Validation of the sterilization process is specified in the applicable sterilization standards (such as for radiation in ISO 11137-1 and for ethylene oxide in ISO 11135-1). Periodic process validation of the sterilizer by the operator/supplier and reports of these validations are required. The pre-qualified IUD manufacturer is expected to monitor this, to obtain and maintain copies of the validation reports and to review them as part of supplier evaluation and control. The IUD manufacturer should include these validation reports in any audits of the sterilization supplier that they carry out. Typically the frequency of such full audits is between one and two years, not more.

4.5 Sterilizer Process Control

The standards provide details on the routine monitoring and control of sterilization processes. For radiation sterilizers this includes the use of chemical dosimeters. Biological indicators, such as bacterial spore strips, and chemical indicators are used for process control of ethylene oxide and other gas sterilizers. All aspects of the effective use of these dosimeters or indicators should be appropriately monitored by the IUD manufacturer for product release and as part of their routine auditing of the supplier. Confirmation of the acceptable levels of sterilizer monitoring should be included in any audits of the sterilization supplier by the IUD manufacturer.

The IUD manufacturer should review and monitor the other controls of the sterilizer specified in the standards. For example, ISO 11137-1 requirements can include:

- Sterilization dose audits to monitor the continued effectiveness of the established sterilization dose and the resistance of the product bioburden to radiation (Clause 12.1.1).
- The frequency of sterilization dose audits shall be based on review and records of the manufacturing process, the control and monitoring procedures for the manufacturing process and, particularly, manufacturing steps that may affect the product bioburden or its resistance (Clause 12.1.3).
- The time interval between dose audits can only be increased if four consecutive dose audits show no change or if the bioburden has remained stable in number and type (Clause 12.1.3.2).
- The maximum dose audit interval is typically one year (Clause 12.1.3.3).
- A dose audit must be completed for every batch if the batch manufacturing interval is greater than the specified dose audit interval (Clause 12.1.3.4).

Manufacturers should note the requirement that “Radiation sensitive visual indicators shall not be used as proof of adequate radiation processing or as the sole means of differentiating irradiated products from non-irradiated products” in respect of terminal radiation sterilization.

Maintaining process effectiveness is specified differently

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1 See Section 9 of both ISO 11137-1 Sterilization of health care products - Radiation and ISO 11135 Medical devices - Validation and routine control of ethylene oxide sterilization
2 See Section 10 of both ISO 11137-1 Sterilization of health care products - Radiation, ISO 11135 Medical devices - Validation and routine control of ethylene oxide sterilization
3 ISO 11135 Medical devices - Validation and routine control of ethylene oxide sterilization
4 See ISO 11137-1 Sterilization of health care products - Radiation - clause 10.4
for each terminal sterilization method. In general, the sterilization standards specify that knowledge of the bioburden on the product is required for conformance according to the standard. The IUD manufacturer shall make it clear to the operator of the sterilization facility that terminal sterilization is a process of joint responsibility. For terminal sterilization by radiation operating according to the standard, monitoring of bioburden is required at a maximum interval of 3 months (or less over time based on historical data) but it is recommended by UNFPA that every Lot should be tested for bioburden.

4.6 Product Bioburden Validation

Manufacturers must maintain product bioburden levels below the validated limit for the sterilization process. This is achieved by a combination of process validation and control.

4.6.1 Scope of process bioburden validation

Bioburden validation of the product shall encompass all of the processes that can directly affect product bioburden. This will include the manufacturing process, manufacturing steps that affect bioburden or its resistance; control and monitoring procedures for the manufacturing process; the manufacturing environment, particularly the extent of microbiological control and monitoring and available data on the stability of the manufacturing environment over time; and the controls on the health, cleanliness and clothing of personnel in the manufacturing area and all other GMP related procedures. Therefore product bioburden cannot be validated in isolation from the process validation and control of those processes that directly affect it.

4.6.2 Development of ‘alert’ (‘warning’) and ‘action’ levels for product bioburden

Acceptable limits for bioburden shall be specified on the basis of previously generated data and shall be documented. If these limits are exceeded, corrective action shall be undertaken. It is therefore recommended that process control of bioburden should be based on setting ‘alert’ (or ‘warning’) and ‘action’ levels (Winters et al). This is considered best practice in the medical device industry. As part of bioburden validation, therefore, manufacturers should establish these limits from historical bioburden data.

In order to establish these levels it is necessary to characterize the distribution of the bioburden and its variability, and obtain appropriate statistically based limits from the data.

The distribution of the product bioburden is established from historical data and more frequent sampling than the recommended quarterly maximum for routine monitoring. Product bioburden samples should be representative of the manufacturing environment and should include, as far as reasonably practicable, samples from just before any routine fumigation and/or other key environmental maintenance operations and the loading of the environment with personnel should reflect normal production levels. Using standard deviations of the data is considered to be a safe assumption that does not necessitate prior consideration of the normality of the data.

In common with normal quality assurance procedures the ‘alert’ level can be set at two times the standard deviations and the ‘action’ level at three times the standard deviations and a limit at 10 times the expected or mean level after the correction factor has been applied (see below). The ‘alert’ level can be set at two standard deviations from the expected mean level since 95.44% of all measurements should fall in this range and the ‘action’ level set at 3 standard deviations since 99.73% of all measurements should fall in this wider range assuming that there has been no shift in the mean.

For established radiation doses, the measured bioburden levels should be compared with the product bioburden limit values specified in the standard.

4.6.3 Correction factor for recovery of microorganisms

ISO 11137-1 (the bioburden standard) requires that during method validation that a correction factor is determined based on the recovery efficiency of the removal of active microorganisms from the product in the process of determining product bioburden. This correction factor is required before the statistics from product bioburden can be safely translated into out of specification limits, to include ‘alert’ (‘warning’) and ‘action’ limits.

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5 See Section 12 of ISO 11137-1 Sterilization of health care products - Radiation, ISO 11135 Medical devices - Validation and routine control of ethylene oxide sterilization and ISO 14937 Validation and routine control of any alternative sterilization process
6 See 12.1.2.1 of ISO 11137-1 Sterilization of health care products - Radiation.
7 See general reference Winters, et al in references list
8 See 12.1.2.1 of ISO 11137-1 Sterilization of health care products - Radiation
9 See general reference Winters, et al in references list
10 See ISO 11137-2 Sterilization of health care products - Radiation Table 5 - Radiation dose (kGy) required to achieve a given SAL for an average bioburden W 1,0
11 See - ISO 11737-1 Sterilization of medical devices - Microbiological methods - sections 3.3, 7.2 b) and C.2.
Examples of how to determine the ‘alert’ ('warning') and ‘action’ levels are provided by Winters et al\textsuperscript{12}. 

### 4.7 Product Bioburden Process Control

UNFPA recommends that product bioburden should be measured on every Lot of product prior to sterilization.

When using the recommended sterilization dose of 25 kGy, ISO 11137-1 states that product is tested for bioburden prior to sterilization at least three months (Clause 12.1.2.2). If the interval between manufacturing of batches is greater than 3 months then every batch must be bioburden tested (clause 12.1.2.4).

#### 4.7.1 Existence of outliers in product bioburden data

The existence of bioburden outliers should be considered and it is recommended that these are investigated before acceptance for inclusion/exclusion with the product bioburden data. If the investigation identifies a problem with the process this should be investigated and remediated before bioburden limits are set.

#### 4.7.2 Purpose and use of ‘alert’ ('warning') levels

The main purpose of the ‘alert’ level is to trigger investigation of the process so that control can be maintained and not necessarily trigger corrective actions or raise issues of product conformity and acceptability for terminal sterilization. The levels may be significantly lower than the limits set in the applicable standard. They are provided to indicate the possibility of significant change(s) in the process. The purpose of ‘alert’ ('warning') levels is to enable the process control to be effective in preventing excursions of product bioburden that could potentially compromise the defined level of sterility assurance.

#### 4.7.3 Purpose of ‘action’ levels

The main purpose of the ‘action’ level is to trigger corrective actions and raise issues of product conformity and acceptability for terminal sterilization. The purpose of the ‘action’ levels is to address the risk of releasing a non-sterile product.

For example, the limits given in the radiation standard\textsuperscript{13} and the statistic of 10 times the expected bioburden level are directly related to the risk of product being non-sterile. Product bioburden results at or above 10 times the expected value limit but well below the limits in the standard must be investigated so that the source of contamination can be identified and assessed. Depending on the source, type and distribution of bioburden, terminal sterilization at the established dose might still be acceptable subject to satisfactory verification that the radiation dose is still effective.

### References

Chapter 4  Bioburden Control and Terminal Sterilization
Chapter 5

Guidance for Stability Studies
5.1 Introduction and WHO/UNFPA Requirements

Stability studies are performed on medical devices to estimate their shelf life under specified storage conditions and permit product expiry dates to be calculated. When conducting stability studies it is essential that fully finished products in their final packaging are used. Changes in packaging can impact on the shelf life of many products. Terminally sterilized products must have been subjected to the full sterilization cycle. Radiation sterilized products must have been subjected to the maximum dose for the maximum period of time specified in the standard operating procedures for the product.

In the case of copper-bearing IUDs, manufacturers must specify the “insert before date”. This is the date from the time of manufacture to the end of the shelf life period derived from stability studies. This confirms that the IUDs will continue to meet all the requirements of this WHO/UNFPA TCu380A IUD Technical Specification up to the time of insertion.

A product’s shelf life can be estimated using accelerated studies but for most products it is necessary to confirm the results of accelerated studies by conducting long-term stability studies at the intended storage temperature. These studies are normally called real-time stability studies. The storage conditions for real time studies have to be determined in advance. The concepts of mean kinetic temperature and world climatic zones, which are discussed in the next section, are extremely useful aids for selecting the storage conditions for real time studies.

Both real time and accelerated stability studies must be carried out on a minimum of three Lots.

5.2 Real Time Stability Studies

Real time stability studies are conducted under a fixed set of storage conditions for the full lifetime of the product. Samples are tested periodically, usually annually, to confirm that they remain in conformance with the Specification. Many characteristics of a product will not change during the storage period whereas other will. It is therefore necessary to identify the critical performance measurements that might change and, if they do, could affect the safety and effectiveness of the product. These critical performance measurements (CPM) need to be monitored during the stability study to ensure that they remain within the specified limits.

For the TCu 380A IUD the critical performance requirements listed below have been identified. These requirements have to be monitored on a periodic basis during the real time stability study:

- T frame breaking strength
- thread tensile strength

Since IUDs are sterile devices it is also essential to monitor the integrity of the individual pouches during real time stability studies. Any failure of the pouch could compromise the sterility of the device. The critical individual pouch measurements (CIPM) that need to be monitored are:

- individual pouch integrity
- individual pouch peel strength

An extremely useful concept used in the pharmaceutical sector for determining the temperature at which real time stability studies should be conducted is the mean kinetic temperature (I). This is a single derived temperature that, if maintained over a defined period, affords the same thermal challenge to a pharmaceutical product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature for a particular storage location can be calculated given knowledge of periodic temperature variations. Many modern temperature data loggers can automatically measure the mean kinetic temperature over a period of time.

Another extremely useful concept from the pharmaceutical sector for determining the conditions for conducting real time stability studies is the division of the world into a set of four climatic zones each with its own defined mean kinetic temperature and average humidity (I). Based on these zones, WHO and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have developed guidelines for conducting long term (i.e. real time) stability studies for pharmaceutical products (2, 3). These recommendations have been adopted by WHO/UNFPA for conducting stability studies on IUDs.

IUDs are intended for distribution and storage on a worldwide basis, with most of the public-sector supply going to hot or tropical countries. Real-time stability studies should be done under the conditions specified for climatic zones III (hot and dry) and IV (hot and humid), both of which have mean kinetic temperatures of 30 °C. For these reasons 30 °C has been set the standard temperature for all stability studies on IUDs intended for WHO/UNFPA prequalification.
In 2006, ICH withdrew Q1F Stability Data Package for Registration Applications in Climatic Zone III and IV because some countries wanted larger safety margins for these zones. The decision was taken to leave the definition of storage conditions for WHO climatic zones III and IV. As a consequence the specified relative humidity for climatic zone IV is now determined by local and regional regulatory authorities. Many have adopted (75 ± 5) % relative humidity rather than the previously specified (65 ± 5) % relative specified in ICH Q1F for climatic zone IV. More information on these changes is given in reference (3). This reference includes a list of countries that have opted to specify (75 ± 5) % relative humidity conditions.

Although relative humidity is unlikely to have any effect on the properties of the IUD directly, pouch seal integrity could be affected depending on the type of polymers used to form the seal. For this reason any new stability studies shall be conducted at (75 ± 5) % relative humidity. Studies at (75 ± 5) % relative humidity shall be initiated upon publication of this revised Technical Specification and Guidance document. Data on studies conducted at 65% relative humidity will remain acceptable until these studies have been completed.

The real-time ageing study shall be commenced at the same time any accelerated studies, using samples drawn from the same production Lots.

The results from the real-time study shall be submitted on its conclusion to interested parties including UNFPA to confirm the shelf life estimate from the accelerated ageing study. Based on real time studies, IUD manufactures may claim an “insert before date” up to seven years from the date of manufacture.

5.3 Accelerated Stability Studies

Accelerated ageing studies are usually carried out at elevated temperatures to force the various chemical processes that are responsible for changes to the product to proceed at a faster rate. Other accelerating factors such as light, humidity and pH can also be used.

Shelf life estimates made at higher temperatures have to be related back to the standard storage temperature of 30°C that has been set for real time studies. This can often be done using the Arrhenius equation describes the relationship between the rate of chemical reactions and temperature (4). The Arrhenius relationship, however, does not apply in all cases. This is why it is still essential to use real time studies to verify shelf-life estimates from accelerated studies.

The Arrhenius equation is usually written as:

\[ k_T = A \cdot e^{-\frac{E_a}{RT}} \]

Where:
- \( A \) = constant \( \text{min}^{-1} \)
- \( E_a \) = Activation energy \( \text{J/mole} \)
- \( R \) = the Universal Gas Constant \( 8.314 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1} \)
- \( T \) = Absolute temperature \( \text{K} \)
- \( k_T \) = the rate constant for the degradation process \( \text{min}^{-1} \).

An alternate way of expressing the Arrhenius equation is:

\[ \ln(k_T) = \ln(A) - \frac{E_a}{RT} \]

The increase in the rate of a chemical process with temperature, as described by the Arrhenius equation, is characterized by a parameter called activation energy \( E_a \). A literature search for the activation energy of polyethylene oxidation during the induction phase, which is considered to be the most likely degradation process that could occur with the TCu380A IUD, found values ranging from 114 kJ/mole to over 200 kJ/mole. These activation energies would lead to the rate of oxidation increasing by at least 4.7 fold (for an activation energy of 114 kJ/mole) to over 15 fold (for activation energies over 200 kJ/mole) as the temperature is raised from 20 °C to 30 °C.

The ageing periods required at different elevated temperatures to provide an equivalent degree of ageing as storage for five years at 30 °C have been estimated using the Arrhenius relationship and an assumed activation energy of 78 kJ/mole. If samples of a product that have been aged at the specified elevated temperatures for these time periods remain within specification, then it is highly probable that the shelf life of the product exceeds five years at 30 °C. Choosing a relatively low activation energy of 78 kJ/mole to calculate the ageing periods at the different temperatures means that the estimated shelf-life will be conservative. In practice, therefore, shelf-lives are likely to be longer than five years at 30 °C if products remain in conformance with the specification at the end of each of the recommended ageing periods and the maximum permitted changes are not exceeded. A full Arrhenius analysis should allow the actual shelf life to be estimated.

Given the intrinsic uncertainties inherent in the interpretation of accelerated stability studies the latest “insert before date” has been restricted to no later than five years from the date of manufacture. For a seven-year “insert

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It can be shown that the time required for the physical properties to deteriorate to a specific threshold value is inversely proportional to the rate constant $k_T$. Plotting the natural log of the times required at different temperatures for a property such as frame strength to fall to the threshold value against the reciprocal of those temperatures (expressed in °K) should therefore result in a straight line if the degradation process follows the Arrhenius relationship. The slope of the straight line will be equal to $E_a/RT$.

To facilitate a full Arrhenius analysis the times required at different temperatures for the physical property that is being monitored to deteriorate to a specific threshold value are determined. The threshold value may be the limit for the property being tested at which the IUD will become nonconforming. Alternatively it may be an arbitrary limit that is sets for convenience, such as fall in strength by 25%. The threshold limit should be chosen such that the time to reach this limit can be determined with a reasonably reliable degree of statistical confidence. It should also be no greater that the maximum permitted change beyond which the product is expected to become nonconforming.

The method recommended in this section for conducting stability studies is based on ISO 11346:2004 Rubber, vulcanized or thermoplastic—estimation of lifetime and maximum temperature of use.

### 5.4 Method of Conducting Stability Studies

#### 5.4.1 Use of standard reference product

If possible a reference product with an established shelf life should be included in the stability study. If a change in specification, raw materials or manufacturing process has been made, then samples of the original product can be used as the reference product. In some cases it may be appropriate to use a competitive product as a reference sample. All the reference samples shall be from the same Lot and shall be within six months of the stated manufacturing date.

#### 5.4.2 Equipment

ISO 188:2007 Rubber, vulcanized or thermoplastic-Accelerated ageing and heat resistance tests, specifies that two methods can be used for conducting stability studies. Method A: Air-oven method uses a cell-type oven or cabinet with low air speed and a ventilation of 3 to 10 changes per hour, whereas Method B: Air-oven method uses an oven or cabinet with forced air circulation by means of a fan and a ventilation of 3 to 10 changes per hour. Ovens or conditioning cabinets should therefore comply with one of these requirements. Whichever type of oven or cabinet is used, it must be consistent from experiment to experiment and within an experiment.

The hygrometer used to monitor the relative humidity shall be accurate to ±2% relative humidity. The calibration of many types of hygrometer can drift significantly over time. It is essential that a calibrated instrument is used. A psychrometer may be used either for direct measurement of relative humidity or as a reference standard for the hygrometer (6). If a psychrometer is used the instrument must be calibrated. See reference (7) for general advice on the selection and calibration of hygrometers.

#### 5.4.3 Test items

Samples from normal production made using normal production equipment and processes (including packaging equipment) and that meet all specification requirements and are within six months of the date of manufacture and sterilization shall be used in testing. Samples shall be in standard packaging.

#### 5.4.4 Use of retained samples

It may be of value to consider using any retained samples that already have been stored for a significant period. These could allow comparison of real-time and accelerated ageing results. Additionally, including such samples would allow evaluation of the effect of accelerated ageing on samples that have already undergone some real-time ageing.

#### 5.4.5 Test sample size

It is strongly recommended that additional samples be included in the study to allow for re-tests and mistakes. When estimating the number of additional samples, the manufacturer should allow for at least one re-test at each temperature, using a sample size with an acceptance number of one or more.

#### 5.4.6 Example test protocol

Table 5.1 lists a set of ageing periods at different temperatures that can be considered equivalent to storage at 30 °C for periods of 1 to 7 years in annual increments. These periods were calculated using the Arrhenius relationship and assume an activation energy of 78 kJ/mol. The times have been rounded up to the nearest week. The relative humidity (RH) for the accelerated ageing and real-time studies shall be maintained at (75 ± 5) % RH. At elevated temperatures a humidity of at least (75 ± 5) % RH at the ageing temperature shall be maintained.
Appropriate combinations of these times and temperatures can be selected when designing stability studies. For example, by measuring how the critical properties of the IUD change over time at three different temperatures, a full Arrhenius analysis of the data can be made as described in Chapter 3. Critical performance measurements (i.e. T frame breaking strength and thread tensile strength) should be measured at each time interval for the specific temperatures selected. It is only necessary, however, to measure the critical individual pouch measurements (i.e. pouch integrity and pouch peel strengths) at the time periods for the selected temperatures that are equivalent to 5 years at 30°C to confirm a 5 year shelf life and 7 years at 30 °C to confirm a 7 year shelf life.

Table 5.1 also includes the recommended annual time intervals and tests required for the real time study at 30°C. Critical performance measurements and critical individual pouch measurements should be completed at each time point in the real time study.

Once a full Arrhenius analysis has been conducted the time periods can be recalculated based on the actual activation energy derived from the Arrhenius relationship. This makes it easier to carry out further stability tests if necessary, for example following changes to the product, manufacturing process or packaging, since a further Arrhenius analysis is unnecessary and a single temperature can be selected from the amended table to very shelf life claims.

### 5.4.7 Measurements

The measurements shall include full packaging and finished product characterization as per this revised WHO/UNFPA TCu380A IUD Technical Specification. Strength measurements are carried out using the amended “arms-up” method outlined in the Technical Specification. The IUD frame in the “arms-up” configuration and the thread (suture) shall be tested independently. Elongation at break shall be recorded and reported.

Results shall be produced from a portion of the original sample immediately before ageing to establish the baseline from which changes are measured.

Biocompatibility and sterility measurements should not be repeated.

### 5.4.8 Significant change

All test results shall be in conformance with this revised WHO/UNFPA TCu380A IUD Technical Specification, using the sampling plan specified. Any results failing to comply with the Specification or showing 25% or greater change from the initial values shall be deemed significant.

A 25% or greater fall in IUD frame strength, thread strength or pouch peel strength shall be taken as an indication that the acceptable shelf life of the product and individual pouch has been exceeded even if these properties comply with the Specification.
5.4.9 Tarnishing
Tarnishing can be expected. If it occurs, it should be noted. There is no evidence that tarnishing affects the shelf life or performance of the product, but excessive tarnishing could cause the product to be rejected by the purchaser or end user.

5.5 Test Results Reporting

5.5.1 Test results
Results shall be reported for the real-time and accelerated ageing product at all the temperatures and times specified. Sample sizes, environmental and ageing conditions, equipment and test methods shall all be referenced.

Records shall be included on any features of note, such as effects on the packaging and product, whether or not reflected in the results, and any testing conditions or events, whether or not it is believed that they affected the results.

The results shall be evaluated statistically and reported in terms of the estimated shelf life with associated estimates of uncertainty.

5.5.2 Sample estimates
Sample sizes shall be equal to or greater than 13. The sample mean and standard deviation shall be reported as well as the number of non-conform samples.

5.6 Estimating the Shelf-Life

Depending upon the outcome of the stability study, different procedures can be used to estimate the shelf life of the product.

- No significant changes are seen in the critical performance measurements at the maximum recommended storage time at each ageing temperature.

In this case it will not be possible to estimate the actual shelf-life of the product, but the maximum time periods have been selected on a very conservative basis to provide a high level of confidence that the shelf-life is in excess of five years at 30 °C if no changes are seen during the accelerated study. If there are no significant changes, then it can be concluded with a high degree of confidence that the shelf life is in excess of five years.

- Significant changes are seen in the critical performance measurements at three or more ageing temperatures, but these are below 25%.

As long as significant changes are seen at three or more of the temperatures chosen for the stability study, then a full Arrhenius analysis can be carried out as described in ISO 11346. For full details on how to do this, refer to ISO 11346. Briefly, the natural logarithms of the times required at each temperature for the critical performance measures to deteriorate to the selected threshold value are plotted against the reciprocals of each temperature (expressed in °K).

If a linear Arrhenius plot is obtained, then it will be possible to estimate the shelf-life at 30 °C with a reasonable degree of confidence by determining the time required for the critical performance measures to decrease by 25% or reach the specified threshold values, whichever occurs earlier. It may be necessary to estimate these times by extrapolation (projecting the curve or line beyond the limits of the data) or interpolation (projecting between data points).

If the Arrhenius plot is not linear, then consider using the WLF (William Landel-Ferry theory, also known as the time/temperature superposition equation) procedure, as described in ISO 11346. (Assistance will probably be required to do this analysis.)

- A critical performance measurement deteriorates by 25% or more within the times periods specified in Table 5.1.

If a critical performance measurement does not comply with the Specification or falls below 25% of the initial value before the maximum duration in weeks at any given temperature, then the shelf-life of the product may be less than five years at 30 °C. An Arrhenius plot should be constructed using 25% as the threshold limit for deterioration, and an appropriate shelf life calculated. In some cases it is expected that the estimated shelf life will be less than five years at 30 °C, but this depends upon the actual activation energy estimated from the Arrhenius plot and whether the plot is linear. It is possible that some degradation processes may occur only at the higher temperatures used in the study and, therefore, not contribute to deterioration of the product under normal storage conditions. If a very marked temperature-dependent effect is observed, then validation of the provisional shelf-life estimate by a real-time study becomes particularly important.
Chapter 5  Guidance for Stability Studies

References
- ICH Tripartite Guideline Q1A(R2), 2003, Stability testing of New Drug Substances and Products.
- EN 455-4 Medical gloves for single use - Part 4: Requirements and testing for shelf-life determination.
- ISO 11346 Rubber, vulcanized or thermoplastic - Estimation of lifetime and maximum temperature of use.

Applicable Standards
- EN 455-4 Medical gloves for single use - Part 4: Requirements and testing for shelf-life determination.
- ISO 7439 Copper-Bearing Intrauterine Devices
- ISO 188 Rubber, vulcanized or thermoplastic - Accelerated ageing and heat resistance tests.
- ISO 11346 Rubber, vulcanized or thermoplastic - Estimation of lifetime and maximum temperature of use.
- WHO Working document QAS/06.179 (Restricted). Stability testing of active substances and pharmaceutical products.
- ISO 13485 Medical devices - Quality management systems -Requirements for regulatory purposes.
- ISO 10012 Measurement management systems - Requirements for measurement processes and measuring equipment.
Annex I
Technical Basis Paper

1 Introduction

The purpose of this technical basis paper is to detail the technical issues that needed to be addressed when updating the 2010 version of the WHO/UNFPA Specification for the TCu380A IUD, which was based on the original Population Council Specification for copper-bearing 380A intrauterine devices IUD dating from the early 1980s (http://bib.muvs.org/data/mvs_000082/volume_2.pdf).

Modern copper-bearing intrauterine devices (IUDs) are a popular, safe and highly effective method of long-term, reversible contraception. The percentage of women experiencing unintended pregnancy within the first year of typical use is 0.8%, and the percentage of women continuing use at one year is 78%[3]. IUDs do not interfere with sexual intercourse and, since they do not require any action on the part of the user, such as insertion immediately prior to intercourse, they are unlikely to be subject to user failure. Once inserted, they can be left in place for between 10 to 12 years, depending upon the type of IUD used. IUDs are relatively inexpensive to manufacture and widely available. It was estimated that in 2007 approximately 163 million women used IUDs, which is 23% of all users of contraceptives[6].

Plastic IUDs were first introduced to the market in the late 1950s and early 1960s (the Lippes Loop, Margulies Spiral and Safe-T-Coil, etc.). Towards the end the 1960s it was discovered that adding copper improved the effectiveness of the IUD and reduced the frequency of problems associated with bleeding. The first copper-bearing IUDs (Copper-7, TCu200 and Nova T) appeared in the early 1970s. These products required replacement every two or three years, but second-generation copper-bearing IUDs introduced towards the end of the 1970s with larger quantities of copper not only reduced the incidence of side-effects but also significantly improved contraceptive efficacy rates. Among the better-known examples of these second-generation IUDs are the TCu380A, TCu220C and Multiload-375 (MLCu375).

The mid-1980s IUDs suffered a loss of popularity when an association between the use of the Dalkon Shield, a plastic non-copper-bearing IUD, and septic abortions (i.e. abortions or threatened abortions associated with pelvic infection) was reported[3], and a case-control study in the USA[4] concluded that Dalkon Shield users were five times more likely to suffer from pelvic inflammatory disease than users of other intrauterine devices. The increase in risk associated with the Dalkon Shield has been attributed to its multifilament thread acting as a wick, allowing bacteria to enter the uterus[5] although this explanation is not universally accepted. Since that time copper-bearing IUDs have continued to be used and have proved to be highly effective and safe.

2 Factors Affecting the Safety and Efficacy of Copper-Bearing IUDs

Copper-bearing IUDs come in a variety of shapes but most usually they have a 'T' or 'horseshoe' shape and are kept in place within the uterus by the extended arms. Frameless designs are also available; these are anchored to the wall of the uterine fundus. Copper-bearing IUDs usually consist of a plastic body around which a copper wire is wound. In some devices the copper wire has a silver core, which is claimed to delay fragmentation and increase the lifespan of the device. Initially, the copper was wound around the vertical stem only, but in more recent designs copper sleeves have been added to the horizontal arms to increase the surface area of copper[6].

A Cochrane Review[7] of the effectiveness and safety of copper-containing IUDs was published in 2006, then updated in 2007 and 2008. The review was prepared by the Geneva Foundation for Medical Education and Research, the Leiden University Medical Centre, the Westminster Primary Care Trust London and the WHO Department of Reproductive Health and Research.

The purpose of the systematic review was to compare different framed copper IUDs for their effectiveness and side effects, including evidence on the possible association between IUD use and pelvic inflammatory disease. Multiple electronic databases were searched in order to identify relevant trials in all languages. A total of 748 citations and abstracts were identified and assessed against the inclusion criteria. Only randomized, controlled studies reporting on clinical outcomes were considered. Of the citations reviewed, 87 met these criteria and were formally assessed using rigorous quality criteria. The final review analysed 42 studies. These 42 reports comprised 34 individual trials involving nine different IUDs, resulting in 16 comparisons involving more than 50,000 women.

Of the IUDs considered in the review, the TCu380A had a lower pregnancy rate than the MLCu375, MLCu250, TCu220C and TCu200. The TCu380S, in which the position of copper on the arms has been changed relative to those of the TCu380A, did not exhibit improved efficacy. The MLCu375 was no more effective in preventing pregnancy than the NovaT at one year, the MLCu250 at three years or the NovaT at three years. Compared with the TCu380A, none of the IUDs reviewed showed any better performance
in terms of bleeding or pain or any of the other reasons for early discontinuations, except the TCu200, which had fewer removals for bleeding and pain in the first two years of use. The TCu380A was therefore preferred over the MLCu375, MLCu250, TCu220C, TCu200 and Cu-Safe 300, and indirect evidence suggested that it performs better than the NovaT and Cu7. There were no published data to support use of the NovaT380. Current devices requiring smaller inserter tubes may have an advantage for the minority of women who have a tight cervical canal. However, these devices may be associated with lower efficacy.

Following publication of the Cochrane Review, WHO/UNFPA convened an IUD Technical Review Committee Meeting to consider the findings of the review and the implications for public health. International experts and researchers in the field of IUDs together with the convenor of ISO/TC 157 WG3 (the international standards committee responsible for developing the international standard for copper-bearing IUDs (ISO 7439), and other representatives of ISO/TC 157 (the international standards committee responsible for non-systemic contraceptives and STI barrier prophylactics), the authors of the Cochrane Review and representatives from WHO Secretariat attended the meeting, which was held on 19-20 September 2007 in Geneva.

After considering the Cochrane Review, the IUD Technical Review Committee reached the following conclusions:

- For a given IUD design there is a trend towards greater efficacy with increased nominal surface area of copper on framed devices.
- The evidence indicates that in general copper on the arms of an IUD improves IUD efficacy.
- Only one comparison allowed consideration of the frame design per se. In this comparison, MLCu250 versus NovaT200, there was no difference in efficacy.
- Surface area and placement of copper on framed devices appears to be more important than the shape of the device.
- There is insufficient evidence to address whether a shorter vertical stem offers any advantage in nulliparous women.
- The Cochrane Review did not include information on the insertion device. Further investigations are required to measure the insertion device against the specifications set by the original manufacturer.
- There was no evidence in the Cochrane Review that the relative performance of different framed copper IUDs varies between age groups.
- There is no evidence that any particular framed copper device is better suited to nulliparous women.
- No framed copper device showed consistently lower removal rates for bleeding and pain than other framed copper devices.
- Other than the Cu7, expulsion rates of framed devices reviewed did not appear to depend on the design of the device or copper loading.
- In the trials reviewed, there was no evidence that any one framed copper device is associated with a greater risk of ectopic pregnancy than others. However, data from other studies indicated that higher copper load devices showed a lower risk of ectopic pregnancy.
- There was no evidence that any one framed copper device was associated with a greater risk of discontinuation for pelvic inflammatory disease (PID).

Also, the Technical Review Committee agreed to make the following recommendations to ISO/TC 157 WG3 to be taken into consideration in the international standard for copper-bearing IUDs (ISO 7439):

- Clinical performance criteria should be those that can be measured objectively. These include pregnancy and expulsion rates, as stated in ISO 7439, Section 4.2.
- Overall discontinuation rates are important indicators of performance that should be considered.
- The requirement on expulsion rates should be modified to state that: “The combined partial and complete expulsion rates should be less than 10/100 during the first year as calculated by life-table analysis.”
- Based on the evidence reviewed, both the point estimates and the upper 95% confidence intervals of the one-year pregnancy rates for two devices, the TCu200 and Cu7 (no longer available), were reported to have exceeded 2.0 per 100 women.
- Eliminate use of the Pearl Index and adopt only single decrement life-table analysis.
- No framed copper IUDs in this review exceeded the requirement on expulsion rates.

Specifically, an IUD for public distribution shall meet the following clinical performance requirements:

- The upper limit of the two-sided 95% confidence interval for the one-year pregnancy rate computed using life-table methods shall be less than or equal to 2%.
- One-year expulsion rates computed using life-table methods shall be less than or equal to 10%.
- One-year discontinuation rates computed using life-table methods shall be less than or equal to 35%.
A number of other recommendations to ISO/TC 257 WG3 concerning the revision of the international standard ISO 7439 were also agreed, including the need to increase the length limit of the device to 36.2 mm, the width to 32.3 mm and to decrease the tensile force (breaking strength) to 9.5 N to accommodate the Specification for the TCu380A IUD. A full list of the recommended amendments to ISO 7439 were published. Following the recommendation made by the Technical Review Committee, ISO 7439 was revised and the second edition of the standard was published in 2011.

The Technical Review Committee also agreed that a revised Specification for the TCu380A device should be developed. The revised WHO/UNFPA Specification was published in 2010.

### 3 The TCu380A IUD

The TCu380A IUD was developed jointly by the Population Council and the FEI (FEI Women’s Health LLC and FEI Products LLC)\(^9\). The Population Council is an international non-profit, nongovernmental organization that seeks to improve well-being and reproductive health. FEI is a women’s health care company specializing in the manufacture and marketing of intrauterine contraception. The first IUD developed by the Population Council in 1967 was made from plastic in the shape of a T. This was followed by the Copper T 200 (TCu200); the first of the copper T family of IUDs. Further development led to the TCu380, which has copper collars on the horizontal arms and copper wire coiled around the vertical stem. The final commercial product of TCu380, packed together with insertion tube and insertion rod in a pouch and treated with terminal sterilization, was marketed as the TCu380A. The United States Food and Drug Administration (U.S. FDA) approved the TCu380A for marketing in 1984.

The TCu380A IUD is made of polyethylene with barium sulphate added for X-ray opacity. It has a solid copper sleeve on each of its two transverse arms, each of which has a surface area of 35 mm\(^2\), and copper wire of 310 mm\(^2\) surface area wound tightly around the vertical stem. The device is 32 mm wide and 36 mm long, with a plastic ball at the bottom of the vertical stem to guard against cervical penetration. A clear or colourless polyethylene filament is tied in a knot through the ball to provide two marker threads.

### 4 The Population Council Specification

The Population Council Specification for the TCu380A IUD specifies the materials, dimensions and properties of the device. The Specification was submitted to the U.S. FDA in NDA 18-680 (Copper T Model TCu380A Intrauterine Contraceptive) and forms the basis of the approval for the product. The Specification requirements are summarized in Annex II.

#### 4.1 Frame

The frame is made from low-density polyethylene (LDPE). The Population Council Specification specify DuPont 20, a specialty low-density polyethylene resin with a low melt index and intermediate crystallinity. The manufacturer states that the polymer is produced by a unique polymerization process and that it has outstanding flexibility and environmental stress crack resistance. It was also claimed to be a “clean” grade suitable for medical use. Other requirements of the Population Council Specification for the polymer are: density 0.906 to 0.929 (units not specified); identification by infrared spectrum (the spectrum included in the Specification is in fact for Alathon 2005); and that the material passes US Pharmacopeia (USP) class II extraction limits for plastics.

Typical values for the physical properties of DuPont 20 as published by the manufacturer are given in Table A1.

<table>
<thead>
<tr>
<th>Property</th>
<th>Nominal value</th>
<th>Test method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
<td>0.92 g/cm³</td>
<td>ASTM D792</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISO 1183</td>
</tr>
<tr>
<td>Melt index</td>
<td>1.9 g/10 min (190 °C/2.16 kg)</td>
<td>ASTM D1238</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISO 1133</td>
</tr>
<tr>
<td>Melting point</td>
<td>108 °C (226 °F)</td>
<td>ASTM D3418</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISO 3146</td>
</tr>
<tr>
<td>Vicat softening point</td>
<td>94 °C (201 °F)</td>
<td>ASTM D1525</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISO 306</td>
</tr>
<tr>
<td>Freezing point</td>
<td>92 °C (198 °F)</td>
<td>ASTM D3418</td>
</tr>
<tr>
<td>Flexural modulus</td>
<td>157 MPa (22,771 psi)</td>
<td>ASTM D790</td>
</tr>
<tr>
<td>Tensile elongation at break</td>
<td>600%</td>
<td>ASTM D638</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISO 527-2</td>
</tr>
<tr>
<td>Tensile strength at break</td>
<td>16.1 MPa (2335 psi)</td>
<td>ASTM D638</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISO 527-2</td>
</tr>
<tr>
<td>Durometer hardness (Shore D)</td>
<td>49</td>
<td>ASTM D2240</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISO 868</td>
</tr>
</tbody>
</table>

In a separate summary table the Population Council Specification specifies that the LDPE should comply with ASTM D1248 Type 1, Class A, Category 3. The standard referred to is undated, but it is probably an earlier version of the current standard, ASTM D1248-05 (the table itself is also undated). ASTM D1248-05 covers polyethylene extrusion plastic materials for wire and cable. Type 1 signifies that the density should be in the range of 0.910 to 0.925 g/cm³; Class A signifies that...
the polymer should be natural in colour; and Category 3 signifies that the melt flow index should be in the range > 1.0 to 10 gram per 10 minutes at 190 °C with a 2.16 kg load. The “grade”, which in ASTM D1248 determines the specification limits for physical properties including tensile strength, elongation at break, resistance to environmental stress cracking and brittleness temperature, is not specified. There is clearly a small inconsistency between the density range specified in ASTM D1248-05 for Type 1 polyethylene (0.910 to 0.925 g/cm3) and the range quoted by the Population Council Specification (0.906 to 0.929).

In order to make the device opaque to X-rays and so facilitate detection within the body, the Population Council Specification that the moulding powder for the frame shall contain between 20% and 24% barium sulphate. USP grade barium sulphate from Picker Corporation Nuclear Department is specified. The amount of barium sulphate is determined by a standard USP method (ash determination).

There is a requirement that frames made from each new Lot of moulding powder should be tested for tissue reactions by intramuscular implantation in two rabbits for at least 72 hours. Animal testing on a routine production basis of this type is still used in certain cases – for example the rabbit pyrogen test for determining endotoxin levels for injectable purposes if different grades or materials or perhaps materials from different manufacturers are used.

A test and requirement for frame flexibility was specified in the original Population Council Specification. However, inadequate details were given about the equipment and test method. Following discussions with manufacturers, an improved description of the test method has been included in this updated WHO/UNFPA TCu380A Technical Specification Guidance, along with a photograph of an example of the test equipment used.

The methodology of this test was reviewed and, after clarification, has been retained.

There is no strength requirement relating to the attachment of the arms to the frame. The amount of recovery achieved (memory) when the arms are folded to a specified angle for five minutes is also unspecified.

There was no discussion in the Population Council Specification relating to moulding defects such as moulding flash, etc., nor were there any limits set for obvious visual defects. These have now been added to the WHO/UNFPA TCu380A IUD Technical Specification from 2016.

4.2 Copper

In the Population Council Specification the copper wire is referred to as Grade 1 PDOF level of impurities (99.99% pure). It is not clear what the designation PDOF means, but it is probably Phelps-Dodge Oxygen Free (Phelps Dodge Mining is a major copper producer). It is also not clear which standard or specification the “Grade 1” refers to, but it is probably ASTM B170-99 (2004). Grade 1 copper is also designated C1000 according to the unified numbering system (UNS) developed by the United States National Bureau of Standards and has a purity of at least 99.99%.[9] It is the highest purity oxygen-free electronic (OFE) copper. Equivalent grades are C1101 in Japan; C101 in Britain; Cu-c2 in France; Cu-OFE in many other parts of Europe including Switzerland, Britain, Italy, the Netherlands, Portugal and Hungary; Cu 99.97B in Poland; Moob in Russia; and OFE in Australia. Some care has to be exercised when looking at designations according to different standards and countries. For example, the British designation C110 is equivalent to UNS C1000 and not to UNS C1000.

The oxygen content of the copper was not specifically stated in the Population Council Specification, but a maximum limit of 0.0005% is specified for C1000 and equivalent grades. This limit for oxygen content was therefore added to the specification for copper. The most commonly used grade of copper for electrical wiring is UNS C1000 (also known as Electrolytic Tough Pitch, or ETP), which is 99.90% pure. It is unlikely therefore that ordinary off-the-shelf copper wire will meet the purity requirements specified. Limits on specific impurities are listed in this Technical Specification (see 7.3, appended table). Assuming that a copper of purity 99.99% is required, then it is necessary to specify UNS C1000 copper or equivalent.

The copper tube used for the collars is specified as OFHC ½ hard temper 99.99% pure. OFHC stands for oxygen-free high conductivity, but this acronym has now been replaced by OFE. Essentially, therefore, the copper tube is of the same UNS C1000 grade as the wire. The specifications for impurities for the tubing and the wire are identical (see appendix table).

The dimensions of the wire and tubing are specified fully, but there are no requirements for physical properties such as tensile strength, etc.
4.3 Thread

A length of thread (thread or suture) is attached to the base of the device to facilitate removal. In the Population Council Specification a high-density grade of polyethylene, Philips Marlex 6006/6007, with a density in the range 0.959 to 0.969, is specified, whereas in a separate summary table high-density linear polyethylene (ASTM D1248 Type IV, Class A, Category 4 or equivalent) is specified. Again, the standard is undated. Inspection of ASTM D1248-05 indicates that this specifies a natural colour with a density greater than 0.96 g/cm³ and a melt flow index in the range > 0.4 to 1.0 g/10 minutes (190 °C, 2.16 kg load). Again, the “type” is not specified, hence neither are the physical properties of the thread.

The Population Council Specification states that the thread can contain up to 1% titanium dioxide (no lower limit is specified), whereas the separate summary table specifies 2% to 4% titanium dioxide. A supplier for the thread is specified (Albany International, Canada). Dimensions (thickness and length) are specified (see Annex II), and there is a strength test to ensure that the thread and/or thread attachment meet a specified minimum.

The Population Council Specification states that an intramuscular implantation test in rabbits should be conducted on each LOT of thread. This again raises the issues discussed earlier concerning the frame.

4.4 Insertion instrument

The insertion instrument comes in three parts, according to the Population Council Specification: a solid rod of polypropylene (with 0.5% titanium dioxide added as a colorant), an insertion tube made from polyethylene (density 0.959 to 0.969 according to ASTM D1505-85) and a flange made from PVC containing titanium dioxide and FDC Blue #1. There are no requirements relating to the specific grades of these materials, nor to the amount of titanium dioxide and blue pigment added to the flange in the main Specification. The summary table specifies the same ASTM D1248 requirements for the polyethylene tube as for the thread and states “medical grade” for the PVC. Dimensions are specified adequately for the rod, insertion tube and the diameter of the hole on the flange, but there is no requirement for the shape and outer size of the flange. There are no requirements covering the physical properties of the insertion device other than the force required to displace the flange, which should be in the range 0.46 lb to 2.0 lb. Failures below the 0.46 lb limit are classified as major defects, whereas those over the upper limit of 2.0 lb are classified as minor defects.

4.5 Packaging

The packaging specified in the Population Council Specification is clearly intended for ethylene oxide sterilization and as such has to be permeable to gas and moisture but still function as a microbial barrier. A laminated polyethylene and Mylar polyester film (Tower 1411 or 1440) is specified for one side and Tyvek 1073B (American Converters/Tower of Mundelein or Rexham Health Care Packaging) for the other side. The thicknesses of the polyethylene and Tyvek are specified, but it is not clear if the original Specification refers to the polyethylene component alone or the total laminate thickness.

For a sterile medical device, such as an IUD, it is critical that pack integrity and pack seal strength are adequate. The Population Council Specification requires visual inspection of the pack seal during manufacture and a pressure test using proprietary equipment (ARO automatic Test-A-Pack System) on a minimum sample of 32 packs taken from each Lot (or 1 per 800 finished units). The sampling scheme is effectively a double sampling plan (2x32) with not more than one pack out of the combined sample of 64 exhibiting a seal rupture when 33 inches of water pressure is applied for a period of 30 seconds. This is equivalent to an AQL of 1.0 (ISO 2859-1). The Population Council Specification states that this test is equivalent to a peel strength test with a minimum tensile strength requirement of one pound per one-inch strip.

Specifications for the packaging of sterile medical devices are covered by the recently published international standards ISO 11607 Packaging for Terminally Sterilized Medical Devices - Parts 1 and 2. Part 1, ISO 11607-1:2006, covers requirements for materials for sterile barrier systems and packaging systems, while Part 2, ISO 11607-2:2006, covers validation requirements for forming, sealing and assembly processes. These new standards harmonize previous ISO and European requirements. The intent of these standards is to ensure that the integrity of the final package is maintained at least for the claimed shelf life of the medical device under the storage conditions specified by the manufacturer. In reviewing the WHO/UNFPA TCu380A IUD Technical Specification, it is important to note any relevant requirements relating to packaging described in these standards.
4.6 Sterilization

The Population Council Specification specifies sterilization by ethylene oxide using terminal testing of Bacillus subtilis spore strips to monitor the process (biological indicator). Limits and testing methods for ethylene oxide residues (ethylene oxide, ethylene chlorohydrin and ethylene glycol) are specified. There are no requirements relating to bioburden levels prior to sterilization nor are there any requirements to validate the process.

Until very recently ethylene oxide sterilization was covered by two separate standards, ISO 11135:1994, adopted by ANSI/AAMI in the United States, and EN 550 in Europe. These standards have recently been harmonized, and a new ISO standard: ‘ISO 11135-1:2007 Sterilization of Health Care Products-Ethylene Oxide. Part 1. Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices’ has just been published.

Various methods are specified for validating ethylene oxide sterilization. One of the most common is the overkill method, although parametric-release is becoming widely used. Before validation the required sterility assurance level (SAL) should be defined, taking into account the device’s intended use. The SAL is the probability of a single viable microorganism occurring on an item after sterilization, although ageing properties might be compromised. The main components of the IUD are therefore unlikely to be adversely affected initially by radiation sterilization, although ageing properties might be compromised. WHO commissioned a study to assess the long-term service life of the product. This study did not identify any evidence of oxidative degradation occurring in utero. On the basis of this study it is considered unlikely that radiation sterilization has any adverse effect on the service life of the product.

Polypropylene has poor radiation resistance, with a maximum dose tolerance of less than 50 kGy. The insertion rod, which is made from polypropylene, may therefore be adversely affected and as a consequence the shelf life of the product may be compromised. Similar comments apply to the PVC flange, although PVC is more resistant than polypropylene and should be able to tolerate a dose of 50 kGy.

Sterilization by radiation is covered by a series of international standards, ISO 11137-1, 11137-2 and 11137-3. Again, these standards have recently harmonized ANSI/AAMI/ISO and European requirements (EN 552).

The topics covered by these three standards are summarized below:

ISO 11137-1 Specifies requirements for the development, validation and routine control of a radiation sterilization process for medical devices.

ISO 11137-2 Specifies methods of determining the minimum dose needed to achieve a specified requirement for sterility and methods to substantiate the use of 25 kGy or

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2 Note: All references to ISO standards refer to the latest published edition of that standard.
15 kGy as the sterilization dose to achieve a SAL of $10^{-6}$. It also specifies methods of dose auditing in order to demonstrate the continued effectiveness of the sterilization dose.

ISO 11137-3 provides guidance on the requirements in ISO 11137 Parts 1 and 2 relating to dosimetry. Dosimetry procedures are related to the development, validation, and routine control of a radiation sterilization process.

Again, various methods are specified for the validation of sterilization by irradiation, all intended to confirm that a specific radiation dose is effective in achieving the required SAL for a specific product and a specified bioburden limit. Typically, validated processes are controlled by bioburden monitoring and dosimetry rather than by using biological indicators. When conducting validation programmes on medical devices, it is essential to ensure that adequate attention is given to the potential effect of the radiation on the properties and shelf life of the product.

The following international standards also apply in general to the sterilization of medical devices:


ISO 14937 Sterilization of Health Care Products - General Requirements for Characterization of a Sterilizing Agent and the Development, Validation and Routine Control of a Sterilization Process for Medical Devices.

4.7 Product release testing

The Population Council Specification includes the following requirements for testing the finished product prior to release:

1. The amount of wire (by weight) on the T (limits 165 to 178 mg), using a double sampling plan based on an AQL of 0.65 and an Inspection Level of S-4
2. The diameter of the copper collars (0.082 ± 0.001 inches) and the location of the collars on the arms (5.4 ± 0.4 mm from the ends), using a double sampling plan based on an AQL of 0.65 and an Inspection Level of S-4
3. The length of the thread (10.5 to 12.5 cm) on 50 samples
4. The strength of the thread/IUD (2.0 lbs, equivalent to 0.907 kg, or 8.89 N) on a sample of 50 devices, with not more than one device breaking below this limit (equivalent to an AQL of 1.5)
5. Sterility using Bacillus subtilis spore strips containing $10^6$ spores per strip inserted into 10 packages during sterilization and cultured for 10 days
6. Residual ethylene oxide, ethylene chlorohydrin and ethylene glycol by head space GC on 10 samples
7. Pouch burst strength using the ARO automatic Test-A-Pack system on 1 pack per 800 units, with a minimum pack sample size of 32.

5 Discussion Relating to the Original Population Council Specification and development of the WHO/UNFPA TCu380A IUD Specification, 2010

The Population Council Specification adequately specified the TCu380A IUD in terms of base dimensions and basic physical requirements. The requirements complied with the generic requirements specified in ISO 7439:2002. The test methods described in the Population Council Specification relate to specific types of equipment. Consideration had to be given to extending the scope of test procedures to allow a wider choice of equipment to be used. Sample sizes and acceptance/failure criteria were stated explicitly rather than by inspection level and AQL.

Discussions with manufacturers prior to revision of the Population Council Specification highlighted a number of issues relating to the design that needed to be considered. The junctions between the arms and the stem of the device, as specified by the Population Council Specification were sharp right angles and as such would give rise to high stress concentrations whenever the arms were deflected. On the basis of finite element analyses, one manufacturer had elected to eliminate the sharp junctions by adding a radius to reduce stress concentration and, therefore, the risk of the arms breaking off. Such a design change was not considered to affect the efficacy of the device. It was considered by the IUD Technical Review Committee that this change should reduce the risk of failure in utero, although excessively large radii could increase the stiffness of the arms and increase the risk of crush damage when the arms are bent down to load the device into the insertion tube. After reviewing the available information the Committee decided to include recommendations for including radii in the specifications at the junctions.
The specifications for the materials of construction for the device needed to be updated to take into account changes in nomenclature and specifications/standards since the Population Council Specification had been developed. A critical question relating to the choice of materials was whether they should be specified by manufacturer and trade name or by generic description supported by physical properties specification. It was decided that the latter option was preferred.

In general, polyethylenes are prone to oxidation and it is common practice to add antioxidants to these plastics to improve the shelf life and service life of products made from them. Members of the IUD Technical Review Committee found it surprising that antioxidant-free grades of polyethylene were specified by the Population Council Specification and that no antioxidant was added, particularly given the long shelf life and in utero time associated with the TCu380A IUD. The extent to which devices from different manufacturers need to be subjected to safety and biological evaluation was also reviewed, particularly given the proposed move towards making the specifications for materials generic.

One manufacturer had raised questions about the particle size of the barium sulphate and the quality of the dispersion obtained in the plastic. Again, this relates to the risk of detachment of the arms under stress. Excessively large barium sulphate particles or clumping of the particles may lead to excess stress concentrations in the region where the arms join the stem of the device, leading to failure. The use of micronised barium sulphate was recommended along with a qualitative check by X-ray on the uniformity of distribution of barium sulphate within the device. The need to make the device X-ray opaque was questioned, given the current prevalence of ultrasound scanning around the world, but feedback from clinicians clearly identified an ongoing need for IUDs to be detectable by X-ray.

The Population Council Specification did not include a specification for the titanium dioxide pigment used in the thread. Additional comments from manufacturers indicated that many did not know which grade was used, but one suggested that the titanium dioxide must be the rutile rather than the anatase morphology. An appropriate specification for the titanium dioxide needs was therefore developed. DuPont Titanium Technologies recommended a specific grade of titanium dioxide for incorporation into injection-moulded polyethylene/polypropylene, DuPont™ Ti-Pure® R-350, which has a rutile morphology. Some manufacturers and purchasers also specified that the thread should be monofilament medical-grade nylon, since this material is both stronger and produces a thread with a smoother surface than high-density polyethylene.

There was a clear discrepancy between the minimum strength of the device, as specified in ISO 7439, of 12 N (equivalent to 1.224 kg force) and the Population Council Specification of 2.0 lbs, which is equivalent to 8.89 N (0.907 kg force). One manufacturer reported that it was difficult to meet the ISO requirement of 12 N given the specified material and thread diameter. The same manufacturer stated that it was better to retain the lower breaking force specification since it is preferable for the thread to break rather than the body of the device.

Since the Population Council Specification had been developed, sterilization practices had developed considerably, and the requirements and procedures described in the original Specification were considered unacceptable by modern standards. The sterilization requirements were reviewed against the recent harmonization of US and European sterilization practices with the publication of new ISO standards. Requirements for sterilization validation were missing from the current Specification, as were alternative methods of sterility assurance such as parametric release.

Given the prevalence of radiation sterilization among manufacturers, consideration was given to accepting this method as an alternative to ethylene oxide, taking into account any potential adverse effects of radiation on the properties, shelf-life and service life of the product. Following a detailed review and an assessment of used IUDs removed from patients, it was agreed that radiation sterilizations was not only a satisfactory alternative, but because it permitted the use of film-based packaging materials with improved barrier properties, was actually preferred.

The packaging requirements in the Population Council Specification were also reviewed, taking into account the requirements specified in ISO 11607 Parts 1 and 2, packaging for terminally sterilized medical devices, and recent trends in medical device packaging. Consideration was given to the specifications for pouch integrity and seam strength, particularly whether these were adequately specified and assessed. It was recognised that changing to radiation sterilization would allow occlusive film-on-film packs to be used, with the advantage of extra product protection. Some manufacturers had reported that using permeable packs that do not prevent the ingress of moisture could lead to tarnishing of the copper. Film-on-film packs were also considered easier to test for pack integrity since various vacuum-based methods can be used.
The Specification review also took into account manufacturers’ current practices at the time and the extent to which any changes in the materials, construction or even the design of the TCu380A IUD might affect its safety, efficacy and shelf life. Consideration was given to the quality of any validation work undertaken by the manufacturers when changes had been made to the manufacturing processes and materials used.

After considering all of the above issues a revised Specification was developed and published in 2010 as the WHO/UNFPA TCu380A IUD Specification.

6 ISO 7439 Second Edition 2011 Requirements

6.1 New requirements

Following publication of the 2010 edition of the WHO/UNFPA Specification for the TCu380A IUD, ISO 7439 – the international standard for copper-bearing IUDs – was revised and published as a second edition in 2011 (ISO 7439:2011). The standard remained generic in nature, covering all single-use copper-bearing IUDs. Being generic, it specifies relatively broad limits on dimensions (length not greater than 36.2 mm, width not greater than 32.3 mm) and copper content (surface area 200 to 380 mm²). Tolerances specified are ± 5% for dimensions and ± 10% for copper area. The purity of the copper is specified as 99.9% rather than the 99.99% required by the Population Council Specification.

Other requirements include that the thread shall be monofilament, the device and thread shall withstand a tensile force of at least 9.5 N for T-shaped devise and 12 N for all other devices. The insertion instrument shall have a maximum diameter of 5 mm, when deformed the device shall recover to within ± 5 mm of its original shape within one minute, and the device shall be detectable by X-ray (if barium sulphate is used, then its content shall be from 15% to 25%).

ISO 7439 does not specify inspection levels or acceptable quality limits (AQLs). Appropriate inspection levels and AQLs were developed and included in the 2010 WHO/UNFPA Specification for the TCu380A IUD.

In terms of product safety, ISO 7439 requires that the device shall be evaluated in accordance with requirements of ISO 10993-1: Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing. The standard states that supplementary tests for chronic toxicity, carcinogenicity and reproductive toxicity should be considered. ISO 7439 also includes extensive requirements for labelling, instructions for use and information intended for women, none of which is included in the Population Council Specification.

ISO 7439 specifies that the product shall be supplied sterile but gives no guidance on sterilization methods or procedures for assuring sterility, nor does it specify a SAL. Reference is made to Clause 9, ISO 14630 Non-active Surgical Implants - General Requirements.

6.2 Clinical evaluation in ISO 7439

There is a requirement in ISO 7439 for the contraceptive efficacy of a copper-bearing IUD to be determined by clinical evaluation. It was stated in the 2002 edition that the evaluation should meet certain minimum requirements in terms of the total number of menstrual cycles (at least 10,000), the number of women completing (at least 400 for the first year and 200 for the third year) and the in situ time (three years). The requirements for pregnancy and expulsion rates specified in Clause 4.2 of ISO 7439:2002 were as follows:

- “pregnancy rate ≤ 2 per 100 woman-years during the 1st year as calculated by life-table analysis”
- “expulsion rate ≤ 10 per 100 woman-years during the 1st year as calculated by life-table analysis”.

Based on feedback to ISO/TC 157 from the WHO/UNFPA IUD Technical Review Committee which follow the publication of the Cochrane Review, ISO 7439 was amended. The revised clinical performance requirements in ISO 7439:2011 are:

- the upper limit of the 95% confidence level, two-sided confidence interval for the one-year pregnancy rate computed using life-table methods shall be ≤ 2%
- one-year expulsion rates computed using life-table methods shall be less ≤ 10%
- one-year discontinuation rates computed using life-table methods shall be ≤ 35%.

However, larger studies are required to meet these requirements. Therefore, the IUD Technical Review Committee made additional recommendations to increase the size of the study to include at least 20,000 women-months in the group using the new device under test, which can be achieved by conducting a randomized study in which an average of 720 women use the test device in the first year of the study and an average of 360 women in a control arm use the TCu380A device. These recommendations had also been incorporated into ISO 7439:2011 along with notes providing further details about the power and size of studies required to meet the new clinical performance requirements.
The discussions held within ISO/TC 157 to consider the changes proposed by the IUD Technical Review Committee relating to clinical requirements identified the need for more detailed guidance on the design and execution of clinical trials for IUDs. As a consequence a New Work Item Proposal (NWIP) was submitted by ISO/TC 157 in 2011 to develop a standard for this guidance. The NWIP was approved and development of the standard, to be published as ISO 11249, has been progressing under the direction of ISO/TC 157 WG20 - Clinical Trials. The standard has reached the DIS stage (Draft International Standard).

The TCu380A IUD has already undergone extensive clinical evaluation, and the Technical Review Committee, based on the outcome of the Cochrane Review, concluded that not only does the device meet the current performance requirements of ISO 7439:2002, but it also meets proposed amendments to the standard. The review concluded that the pregnancy rate for the TCu380A IUD was in the range 0 to 1 after one year per 100 women, and the expulsion rate was in the range of 2.4 to 8.2 after one year per 100 women.

7 Discussion Relating to the Revision of the 2010 WHO/UNFPA TCu380A IUD Specification

A meeting of the WHO/UNFPA/FHI360 IUD Technical Review Committee was convened in Geneva on 16 to 19 September 2013, primarily to review the draft Specification for the TCu375 IUD. The Committee also reviewed the 2010 TCu380A IUD Specification, Prequalification and Guidelines for Procurement to address a number of technical issues that had arisen relating to the Specification and to review the challenges and lessons learned following publication of the document. The meeting confirmed that there were a number of issues that needed to be addressed and it was agreed that a revised edition of the Specification would be developed. The main reasons for the revision are summarised below:

- The layout of the Specification was considered confusing and lacking in clarity. Manufacturers and procurement agency staff found the document difficult to navigate and interpret.
- There was confusion between manufacturing and purchase elements of the Specification; it was not clear which tests were required for prequalification purposes and Lot-by-Lot release testing of the finished products and which tests related to components only and should therefore be entirely the responsibility of the manufacturer.
- Significant problems had been encountered when trying to sample Lots for prequalification testing. Insufficient Lots were often available to permit sampling to be conducted according to the specified procedures. Even when Lots were available these were often too small to permit the full complement of samples to be taken.
- There was a lack of clarity about the sample sizes required for both prequalification testing and Lot-by-Lot release testing. Sample sizes required for Lot-by-Lot release testing by manufacturers or compliance testing by purchasers were considered excessive for many of the test requirements. Given the nature of the manufacturing processes used to make IUDs, a very high level of within Lot consistency can be expected. This factor had not been adequately taken into account when the original sampling plans had been developed.
- There was considered to be an intrinsic conflict between the specified pouch integrity requirement (AQL 0.65) and the sterility assurance level of 10^-6. Any pouch leaking, which could potentially be as high as 2,500 per million, could lead to microbiological contamination of the IUD contained within the pouch. The need for more stringent limits on pouch integrity were recognized.
- Issues remained with some of the test methods specified in the 2010 version of the WHO/UNFPA Specification.
- Some revisions were required to the procedures and requirements for assessing biocompatibility according to ISO 10993 including clearer directions on the choice of procedures for assessing cytotoxicity.

Following the meeting a number of proposed changes to the Specification were discussed and agreed. The proposed changes were presented to IUD manufacturers and other interested parties including procurement groups at a meeting in Delhi on 18 to 21 February.

Feedback from the manufacturers at the Delhi meeting was extremely useful in addressing the issues that had been raised. As a consequence the revision of the Specification was agreed to address the points raised above. Some minor changes were also made to the Specification relating to dimensions and tolerances to take into account current manufacturing practices. The changes are detailed in the revised WHO/UNFPA TCu380 Intrauterine Contraceptive Device (IUD) Technical Specification and Prequalification Guidance, 2016.
7.1 Sampling plans
As part of the review process an extensive revision of the sampling plans was undertaken to address the issues listed below that had been identified during prequalification testing and manufacturer inspections since the introduction of the Prequalification Programme:

- Lot sizes used in the manufacture of IUDs tend to be significantly smaller than those used for other contraceptive devices such as male latex condoms. This can restrict the number of samples available for testing, particularly when doing surveillance and prequalification testing.
- Many manufacturers work on a demand basis and may not have sufficient Lots available at any specific time to permit the random sampling of three lots for prequalification testing.
- Many of the manufacturing processes used to make IUD components (e.g. injection moulding) operate within a very high degree of precision once set up. Relatively small sample sizes can therefore be used to assess Lot conformance for many IUD properties.

A general decision was made to avoid the use of AQLs and inspection levels when specifying quality requirements. Instead it was decided to specify a fixed sample size and to require there to be no nonconforming IUDs present in the sample when assessed for any specific requirement. Adopting this approach permits the smallest possible sample sizes to be used consistent with achieving a specific quality level. It was also recognised that requiring manufacturers to switch to larger sample sizes if there is evidence of deterioration in quality (see a description of the “switching rules” in ISO 2589-1 for a full explanation) significantly reduces the risk of nonconforming Lots being accepted over the longer term. These principles were used to select the sample sizes specified for Lot-by-Lot testing in routine production.

When fewer than five Lots are being tested in isolation, the switch to the larger sample sizes cannot be implemented. For such situations, for example in surveillance testing when a small number of randomly selected Lots may be tested by a purchaser or testing laboratory, larger sample sizes with an acceptance number of one have been selected (the acceptance number is the maximum number of nonconformities permitted in the sample before the Lot is rejected). Finally, for prequalification testing where a high level of confidence is required in the outcome of the test results a set of sample sizes has been developed with acceptance numbers of at least two.

7.2 TCu380A IUD surface area
One issue that has not been resolved during this revision of the WHO/UNFPA Technical Specification for the TCu380A IUD relates to a small discrepancy in the total copper surface area of the IUD - depending upon the method used to determine this area. The surface area of the wire is based on weight, density and diameter. Given a copper density of 8.96 g/cm², which appears to be the most reliable estimate in the technical literature, the surface area based on the original Population Council Specification is 176 mm².

The original Population Council Specification included requirements for copper collar weights and dimension. Although the collar dimensions can be accurately measured prior to assembly of the device, the swaging or crimping processes used to attach the collars to the arms will distort the dimensions of the collars. Copper collar weight is therefore a more useful control parameter when assessing the conformity of finished IUDs, particularly by third party laboratories carrying out prequalification and pre-release testing.

The surface area of the collars can be calculated from either the dimensions alone (i.e. from the length and outer diameter) or from the weight, density and diameters (both the inner and outer diameters are required). These two methods result in small differences in the total copper surface area of the device (376.2 mm² based on collar weight and diameters and 378.8 mm² based on the collar length and outer diameter). The rounding introduced in the WHO/UNFPA 2010 Specification further increased this discrepancy between the two methods of determining surface area (375.0 mm² when calculated from the collar weight and diameters compared to 388.2 mm² when calculated from collar length and outer diameter). There is therefore a risk of confusion between devices with specified surface areas of 380 mm² such as the TCu380A, and devices with specified surface areas of 375 mm² such as the Cu375, when collar weight is used as the basis for estimating total surface area.

The source of the discrepancy appears to be the original Population Council Specification. The specified collar weight should have been 71.4 mg, not 68.7 mg. The correct specification for the collar weight reduces to 71.0 mg for the rationalised dimensions given in the WHO/UNFPA Specification. Alternatively, the inner diameter specified by the Population Council Specification for the copper collars might have been incorrect. A more detailed review of manufacturers’ dimensional and weight data on the copper collars prior to assembly of the device would assist in identifying the source of the discrepancies, permitting an appropriate correction to the copper collar specification to be made in the future.
### 7.3 Copper purity specification

<table>
<thead>
<tr>
<th>Impurity</th>
<th>Maximum (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag</td>
<td>0.0025</td>
</tr>
<tr>
<td>As</td>
<td>0.0005</td>
</tr>
<tr>
<td>Bi</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cd</td>
<td>0.0001</td>
</tr>
<tr>
<td>Fe</td>
<td>0.0010</td>
</tr>
<tr>
<td>Mn</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ni</td>
<td>0.0010</td>
</tr>
<tr>
<td>O₂</td>
<td>0.0005</td>
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<tr>
<td>P</td>
<td>0.0003</td>
</tr>
<tr>
<td>Pb</td>
<td>0.0005</td>
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<tr>
<td>S</td>
<td>0.0015</td>
</tr>
<tr>
<td>Sb</td>
<td>0.0004</td>
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<tr>
<td>Se</td>
<td>0.0003</td>
</tr>
<tr>
<td>Sn</td>
<td>0.0002</td>
</tr>
<tr>
<td>Te</td>
<td>0.0002</td>
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<tr>
<td>Zn</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

### References

## Summary of Specification Changes

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<tbody>
<tr>
<td>Lot Definition</td>
<td>Not defined</td>
<td>Not specified</td>
<td>A quantity of products, such as IUDs, manufactured under essentially the same conditions. With certain exceptions, all the IUDs comprising a LOT will have single batches of components and be manufactured on the same production line and be sterilized under the same conditions over a single continuous series of dates.</td>
<td>Homogeneous collection of IUDs made under essentially identical manufacturing conditions using the same lots of raw materials; low-density polyethylene (LDPE) compound, high-density polyethylene (HDPE) compound, copper for wire and collars, individual pouches and individual pouch material that are subjected to sterilization in the same sterilization cycle and assigned a unique number before release. Clear Lot identification and recording are required to permit effective product recall in the event of a quality problem with the device.</td>
</tr>
</tbody>
</table>

### Materials

<table>
<thead>
<tr>
<th>T-frame</th>
<th>DuPont 20 polyethylene and (20 – 24)% USP barium sulphate</th>
<th>Shall be visco-elastic, biocompatible and non-absorbable (including the substance conferring radio-opacity)</th>
<th>Low-density polyethylene (LDPE) free of stabilizers having a minimum tensile strength of 13 MPa (ASTM D638 - ISO 527-2) and a 2% secant flexural modulus in the range 133.5 MPa to 180.6 MPa (ASTM D790). The LDPE shall be blended with 15% to 24% USP precipitated barium sulphate with a particle size of 95% less than 10 micron.</th>
<th>LDPE, free of stabilizers and with a minimum tensile strength of 13 MPa (ASTM D638 - ISO 527-2, using a crosshead speed of 50 mm/min and a type 1 specimen bar) and a 2% secant flexural modulus in the range 133.5 MPa to 180.6 MPa (ASTM D790). The LDPE shall be blended with 15% to 25% USP (United States Pharmacopeia) precipitated barium sulphate with a particle size of 95% less than 10 micron.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper wire requirements</td>
<td>Grade 1 PDOF copper 99.99% pure; table of impurities with ppm limits in specification</td>
<td>At least 99.9% pure</td>
<td>Oxygen-free electronic (OFE) 99.99% pure copper (National Bureau of Standards designation UNS C10100)</td>
<td>OFE 99.99% pure copper meeting the National Bureau of Standards designation UNS C10100. There shall be no coating on the wire.</td>
</tr>
<tr>
<td>Copper collars requirements</td>
<td>OF HC copper tubing half hard temper 99.99% pure; table of impurities with ppm limits in specification</td>
<td>At least 99.9% pure</td>
<td>OFE 99.99% pure copper (National Bureau of Standards designation UNS C10100)</td>
<td>Half-hard temper, seamless copper tube made from OFE 99.99% pure copper meeting the National Bureau of Standards designation UNS C10100. There should be no coating on the collars.</td>
</tr>
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## Summary of Specification Changes

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<tbody>
<tr>
<td><strong>Thread requirements</strong></td>
<td>High-density linear polyethylene (high-density polyethylene – Philips Marlex 6006/6007 – containing up to 1% titanium dioxide)</td>
<td>Shall be monofilament, biocompatible and non-absorbable</td>
<td>The thread shall be monofilament made from HDPE, free of stabilizers, having a sufficient minimum tensile strength to produce a thread meeting the specified strength requirement (9.5 Newton). A material with a minimum tensile strength (ASTM D6380, ISO 527-2) of 28 MPa is recommended.</td>
<td>The thread shall be a monofilament made from HDPE, free of stabilizers, with sufficient tensile strength to meet the specified thread breaking force requirement of 9.5 Newton. A minimum tensile strength (ASTM D6380 - ISO 527-2) of 28 MPa is recommended.</td>
</tr>
<tr>
<td><strong>Insertion tube requirement</strong></td>
<td>Philips Marlex 6006/6007 High-density linear polyethylene</td>
<td>Not specified - no sharp edges</td>
<td>HDPE food contact grade</td>
<td>The insertion tube shall be made from HDPE food contact grade.</td>
</tr>
<tr>
<td><strong>Displacement rod</strong></td>
<td>Polypropylene + 0.5% titanium dioxide</td>
<td>Not specified</td>
<td>Food contact grade radiation stable ABS (acrylonitrile-butadiene-styrene polymer) or food contact grade radiation stabilized polypropylene (PP) with a tip diameter of (2.6 ± 0.2) mm</td>
<td>The rod shall be made from food contact grade radiation stable ABS (acrylonitrile-butadiene-styrene polymer) or food contact grade radiation-stabilized polypropylene (PP). Optionally, the insertion rod may be pigmented.</td>
</tr>
<tr>
<td><strong>Positioning flange requirements</strong></td>
<td>Polyvinyl chloride + titanium dioxide + FDC Blue</td>
<td>Not defined</td>
<td>Polymer with adequate radiation stability to function mechanically post-sterilization. Optionally, the flange may be pigmented.</td>
<td>The flange shall be made from a polymer with adequate radiation stability to meet the requirements for flange displacement force specified in Section 3.4.2, Chapter 3 of the Specification after sterilization. Optionally, the flange may be pigmented.</td>
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</table>
## Annex II  Summary of Specification Change

### Summary of Specification Changes

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<tbody>
<tr>
<td>Biocompatibility requirement</td>
<td>T-frame material and insertion tube material must pass extractable test for Class II plastics by USP method (saline and saline-alcohol extracts of sample at 70 °C injected intravenously in mice).</td>
<td>Shall be compatible</td>
<td>The compounded polymer (LDPE plus barium sulphate) shall be evaluated for biological safety in accordance with ISO 10993-1:2003 requirements for mucosal membrane contact devices intended for permanent contact. Specifically, the following testing is required: testing for genotoxicity according to ISO 10993-3; testing for cytotoxicity testing according to ISO 10993-5; Testing for irritation and delayed-type hypersensitivity according to ISO 10993-10; and testing for subacute and subchronic toxicity according to ISO 10993-11. Requirements for animal implant testing on each compounded LOT have been replaced by in vitro cytotoxicity testing.</td>
<td>The compounded T frame polymer (LDPE plus barium sulphate) and thread or compounded thread polymer shall be evaluated for biological safety in accordance with ISO 10993-1 requirements for mucosal membrane contact devices intended for permanent contact. Specifically, the following evaluations are required: genotoxicity according to ISO 10993-3; irritation and delayed-type hypersensitivity according to ISO 10993-11; and cytotoxicity according to ISO 10993-5 subacute. For a specific material it is only necessary to carry out the assessment of biological safety once. The evaluation shall be repeated if there is a significant change to the materials, for example, if the grade or supplier is changed. Manufacturers may continue to use DuPontTM 20 LDPE and Phillips 6007 HDPE without conducting the biocompatibility evaluation.</td>
</tr>
</tbody>
</table>

Thread must pass rabbit implantation test after at least 72 hours (histology compared to strips of USP Negative Control Plastic Standard).

Moulded T frames made from each new lot of moulding powder must not cause unacceptable tissue reactions when implanted intramuscularly in rabbits for 72 hours or more.

Insertion tube must pass extractables test or class II plastics by USP method (saline and saline-alcohol extracts of sample at 70 °C injected intravenously in mice).
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<tr>
<td>Material procurement and control requirements</td>
<td>Not defined</td>
<td>Not specified</td>
<td>Manufacturers shall take appropriate steps to ensure that batches of compounded materials (T frame and thread materials) are not contaminated by any extraneous impurities during compounding operations. Manufacturers shall document and control the procedures for the compounding of the T frame polymer. Where lubricants are used in moulding, the grades shall be “Food Grade” and/or suitable for medical device manufacture. Every new Lot of compounded frame material (LDPE plus barium sulphate) and thread material (HDPE plus titanium dioxide) shall be subjected to in vitro cytotoxicity testing in accordance with ISO 10993-5 Biological Evaluation of Medical Devices - Part 5. Test for in vitro Cytotoxicity. The cytotoxic response shall not be worse than that recorded for the compounded material when originally evaluated for biological safety according to the requirements of ISO 10993-1. The barium sulphate content of the frame material shall be determined according to the relevant clause of ISO 7439. It has been agreed that manufacturers using the original grade of HDPE specified by the Population Council (Philips Marlex 6006/6007) do not need to complete the testing according to ISO 10993, as specified above, until December 2012 (two years from the date of publication of this Specification). After this date manufacturers must have completed the testing.</td>
<td>Manufacturers are responsible for ensuring all operations, including those undertaken by subcontractors, such as material storage, compounding of the frame and thread materials, and moulding are done to acceptable standards as specified below. There should be adequate control procedures and documentation to ensure and demonstrate conformance with ISO 13485. These procedures should ensure that batches of compounded materials (T frame, thread materials) and moulding and extrusion of the components are not contaminated by any extraneous impurities during processing operations. Where lubricants are used in moulding and extrusion, the grades shall be “Food Grade” and/or suitable for medical device manufacture.</td>
</tr>
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TCu380A Intrauterine Contraceptive Device (IUD)  
### Summary of Specification Changes

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<tbody>
<tr>
<td>Material Storage</td>
<td>Not defined</td>
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</table>

The maximum storage period for the frame polymer and the thread is three years from the date of manufacture when stored at temperatures under 30 °C and two years when stored at temperatures between 30 °C and 35 °C. Provided the breaking force of the frame material exceeds 13.5 MPa and the breaking force of the thread exceeds 9.5 N, then the materials may be used for a further three years when stored at temperatures under 30 °C and two years when stored at temperatures between 30 °C and 35 °C.

Materials and components should be stored in a manner in which they are protected from light and high humidity. The storage condition shall ensure conformance with bioburden levels specified for the product. If appropriate, the copper components or other components should be cleaned prior to assembly. Manufacturers shall introduce procedures to monitor and control the degree of tarnish and rough edges on the copper components.

The maximum storage period before retesting of the raw material is required for the frame polymer and the thread is three years from the date of manufacture when stored at temperatures under 30 °C and two years when stored at temperatures between 30 °C and 35 °C. Provided the breaking force of the frame material exceeds 13 MPa (which may be determined by testing moulded frames) and the breaking force of the thread exceeds 9.5 Newton, then the materials may be used for a further three years when stored at temperatures under 30 °C and two years when stored at temperatures between 30 °C and 35 °C.

Every new Lot of compounded frame material (LDPE plus barium sulphate) and thread material (HDPE plus titanium dioxide) shall be subjected to in vitro cytotoxicity testing in accordance with ISO 10993-5 Biological Evaluation of Medical Devices - Part 5. Tests for in vitro Cytotoxicity. See Section 3.6.6. The cytotoxic response shall not be worse than that recorded for the compounded material when originally evaluated for biological safety according to the requirements of ISO 10993-1.
## Summary of Specification Changes

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<tbody>
<tr>
<td>Material processing requirement</td>
<td>Not specified</td>
<td>Not defined</td>
<td>The recycling of injection moulded reclaimed material for the T frame and the thread is NOT permitted.</td>
<td>The recycling of injection moulded reclaimed material for the T frame and the thread is NOT permitted.</td>
</tr>
<tr>
<td><strong>Shelf life, maximum in-situ time and stability</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Shelf life, maximum in situ time and stability</td>
<td>Not specified</td>
<td></td>
<td>IUD shall meet any performance specification given by the manufacturer based on in vitro studies for the complete duration of the declared shelf life. The frame, together with the copper components, shall retain structural integrity and the entire IUD shall withstand the Tensile force of 9.5 N in situ.</td>
<td>IUD shall meet any performance specification given by the manufacturer based on in vitro studies for the complete duration of the declared shelf life. The frame, together with the copper components, shall retain structural integrity and the entire IUD shall withstand the Tensile force of 9.5 N in situ.</td>
</tr>
<tr>
<td>Stability studies requirement</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Real time at 30°C, minimum 65 % humidity.</td>
<td>Real time at 30°C, (75 ± 5)% humidity.</td>
</tr>
<tr>
<td>‘Insert before date’ requirement</td>
<td>Not specified</td>
<td>Not specified</td>
<td>The maximum permitted shelf life for storage of the device prior to insertion is five years. This defines the “latest insertion date” (LID).</td>
<td>The maximum permitted shelf-life for storage of the device prior to insertion is five years (seven years if justified by real time study). This defines the “insert before date”</td>
</tr>
<tr>
<td>Maximum in-situ time</td>
<td>Not specified</td>
<td>Not specified</td>
<td>12 years</td>
<td>12 years</td>
</tr>
<tr>
<td><strong>Sterility and sterilization</strong></td>
<td></td>
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<tr>
<td>Sterilization and method requirements</td>
<td>Ethylene oxide</td>
<td></td>
<td>Sterilization shall be by radiation according to ISO 11137 series or by ethylene oxide according to ISO 11135 series and standards normatively referenced therein. Radiation sterilization is preferred, to allow the use of continuous polymer film packaging materials. The sterilization shall be completed within 30 days of sealing the finished device in the pouch.</td>
<td>The TCu380A IUD shall be supplied sterile in a sealed primary pack together with the insertion tube, the insertion rod and the positioning flange. Sterilization shall be by radiation according to ISO 11137 series, or by ethylene oxide according to ISO 11135 series and standards normatively referenced therein. Radiation sterilization is preferred, to allow the use of continuous polymer film packaging materials. The sterilization shall be completed within 30 days of sealing the finished device in the pouch.</td>
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### Summary of Specification Changes

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<tbody>
<tr>
<td>Sterility assurance level requirement</td>
<td>SAL not specified – assessed by incubation of packages according to USP XXI using 10 packages containing Bacillus subtilis spore strips (106 spores per strip) and 20 standard packages.</td>
<td>Not specified</td>
<td>The sterility assurance level shall be 10(^{-6})</td>
<td>The sterility assurance level shall be 10(^{-6})</td>
</tr>
</tbody>
</table>
| Residual ethylene oxide levels requirement | Mean concentrations must not exceed:  
ethylene oxide 5 ppm  
ethylene chlorohydrin 10 ppm  
ethylene glycol 10 ppm  
No individual sample to exceed:  
ethylene oxide 10 ppm  
ethylene chlorohydrin 20 ppm  
ethylene glycol 20 ppm | Not specified | If ethylene oxide sterilization is used, then residual ethylene oxide levels shall not exceed 10 ppm, and ethylene chlorohydrin levels shall not exceed 20 ppm, on any individual sample when measured using a method that complies with the requirements of ISO 10993-7. Average residual levels across all samples tested shall not exceed 5 ppm for ethylene oxide and 10 ppm for ethylene chlorohydrin. | If ethylene oxide sterilization is used, then residual ethylene oxide levels shall not exceed 10 ppm, and ethylene chlorohydrin levels shall not exceed 20 ppm, on any individual sample when measured using a method that complies with the requirements of ISO 10993-7. Average residual levels across all samples tested shall not exceed 5 ppm for ethylene oxide and 10 ppm for ethylene chlorohydrin. |
| Component dimensions                     |                                                                                     |           |                |                |
| T Frame requirements                     | Length (35.69 – 36.12) mm  
Width (31.62 – 32.26) mm | Nominal Length ≤ 36.2 mm  
tolerance ± 10\%  
Nominal width ≤ 32.3 mm  
tolerance ± 10\% | Length (36 ± 0.5) mm  
Width (32 ± 0.5) mm | Length (36 ± 0.5) mm  
Width (32 ± 0.5) mm |
| Copper wire requirement                  | Diameter (0.254 ± 0.0051) mm  
Weight (165 - 187) mg  
Weight per 100 cm length (436 - 472) mg | Total copper surface area at least 200 mm\(^2\), not greater than 380 mm\(^2\)  
Wire at least 0.25 mm diameter | Diameter (0.255 ± 0.005) mm  
(30 AWG, 33 ISWG)  
Weight (165 - 187) mg | Diameter (0.255 ± 0.005) mm  
(30 AWG, 33 ISWG) |
| Copper collars requirements              | Weight (68.7 ± 3.0) mg  
Length (5.03 ±0.127) mm  
Internal diameter (1.676 ± 0.0254) mm  
External diameter (2.197 ± 0.0254) mm  
External diameter after fixing (2.083 ± 0.0254) mm | Not specified (see copper wire for area). | Weight (68.7 ± 3.0) mg  
Length (5.0 ± 0.15) mm  
Internal diameter (1.68 ± 0.025) mm  
External diameter (2.2 ± 0.025) mm | Internal diameter (1.68 ± 0.025) mm  
External diameter (2.2 ± 0.025) mm  
Length (5 ± 0.15) mm. |
| Thread requirements                      | Length (105 - 125) mm  
Diameter (0.254 ± 0.051) mm | Length not less than 100 mm  
Diameter (0.25 ± 0.05) mm | Length (105 - 125) mm  
Diameter (0.25 ± 0.05) mm | Length (105 - 125) mm  
Diameter (0.25 ± 0.05) mm |
| Insertion tube requirements              | Length (205.05 ±208.224) mm  
Inner diameter (3.70 ± 0.076) mm  
Outer diameter (4.394 ± 0.1) mm  
Density (0.959 - 0.969) g/cm\(^3\) | Max diameter 5 mm  
Tolerance ± 5\% of specification. | Length (206 ± 2) mm  
Inner diameter (3.7 ± 0.1) mm  
Outer diameter (4.4 ± 0.1) mm  
Density not specified | Length (206 ± 2) mm  
Inner diameter (3.7 ± 0.2/-0.1) mm  
Outside diameter (4.4 ± 0.2/-0.1) mm This should be determined using a plug gauge. |

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**Annex II**

### Summary of Specification Change
Summary of Specification Changes

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<tbody>
<tr>
<td>Insertion rod requirements</td>
<td>Length (195 ± 2.54) mm</td>
<td>Not specified</td>
<td>Length (195 ± 2.54) mm</td>
<td>Length (190 ± 5) mm from handle brace to tip. It is recommended that the rod have a thickened section, spline or ridge, to help retain the rod within the insertion tube. The diameter of the insertion rod at tip shall be (2.6 ± 0.2) mm. The rod diameter should be equal to or less than the tip diameter.</td>
</tr>
<tr>
<td></td>
<td>Diameter at tip not specified</td>
<td></td>
<td>Diameter at tip (2.6 ± 0.2) mm</td>
<td>Diameter not specified</td>
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<tr>
<td></td>
<td>Diameter (2.540 - 2.743) mm</td>
<td></td>
<td>Diameter not specified</td>
<td>Diameter (2.540 - 2.743) mm</td>
</tr>
<tr>
<td></td>
<td>Diameter at tip (2.6 ± 0.2) mm</td>
<td></td>
<td>Diameter not specified</td>
<td>Diameter at tip (2.6 ± 0.2) mm</td>
</tr>
<tr>
<td>Flexibility Test</td>
<td>A deflection between 4.8 and 6.5 units at (24 ± 1.5) °C after six hours equilibration and before 96 hours after manufacture with correction factors 0.125 units per °C difference from 24 °C between 20 °C and 29 °C. After 96 hours from time of manufacture, a deflection greater than 4.0 units.</td>
<td>Not specified</td>
<td>Retained, as in Population Council Specification, but narrowing temperature range to (23 ± 2) °C, after careful consideration following clarification of the units as mm and establishing that the test is feasible and the equipment defined.</td>
<td>When tested according to the test method given in Section 3.6.2 the deflection of the horizontal arm measured at the end of the arm shall be greater than 4.0 mm. This test must be performed on frames prior to assembly. Therefore, verification of conformance with this requirement shall be confirmed at prequalification and re-qualification.</td>
</tr>
<tr>
<td>Finished product requirements</td>
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</tr>
<tr>
<td>T Frame</td>
<td>Same as component requirements</td>
<td>Same as component requirements</td>
<td>Same as component requirements</td>
<td>All IUDs measured in a test sample shall fall within these ranges: length of horizontal arms (total length of both arms): (32 ± 1.0/-0.5) mm length of vertical stem: (36 + 1.0/-0.5) mm diameter of horizontal arm: (1.6 ± 0.1) mm. The measurement should be taken between the collars diameter of vertical stem where it is not covered by copper wire: (1.5 ± 0.1) mm. • The vertical stem shall terminate in a ball. The T piece ball (at the end of vertical stem) shall have a diameter of (3.0 ± 0.7) mm. The junction between the ball and the vertical stem shall preferably be radiused. • The T piece ball (at the end of vertical stem) shall have a hole for securing the thread.</td>
</tr>
<tr>
<td>Thread</td>
<td>See breaking force specification</td>
<td>Same as component requirements</td>
<td>Same as component requirements</td>
<td>The thread shall be knotted to form two tails of approximately equal length. The length of each tail shall be not less than 105 mm and not greater than 125 mm.</td>
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## Summary of Specification Changes

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<tbody>
<tr>
<td><strong>Copper Collars</strong></td>
<td></td>
<td>Same as component requirements</td>
<td>Same as component requirements</td>
<td>Collar position: (5.4 ± 0.4) mm from the ends of the T horizontal arm. The measurement shall be taken from the ends of the arms. Collar weight shall be (68.7 ± 3.0) mg.</td>
</tr>
<tr>
<td>Diameter (2.083 ± 0.025) mm</td>
<td></td>
<td>(5.4 ± 0.4) mm from the ends of the horizontal arms of the T</td>
<td>Collar position: (5.4 ± 0.4) mm from the ends of the T horizontal arm. The measurement shall be taken from the ends of the arms. Collar weight shall be (68.7 ± 3.0) mg.</td>
<td></td>
</tr>
<tr>
<td><strong>Copper Surface Area</strong></td>
<td>Same as component requirements</td>
<td>Total copper surface area at least 200 mm², not greater than 380 mm², Wire at least 0.25 mm diameter</td>
<td>The total nominal active copper surface area, wire and collars, shall be 380 mm² ± 10% The nominal surface area shall be 380 mm² with a tolerance of ± 10% (tolerance specified in ISO 7439). Provided the copper collar and copper wire weights are within the Technical Specified limits below, the surface area will comply with the requirements of this specification and ISO 7439 tolerances. Collar weight shall be (68.7 ± 3.0) mg. Wire weight shall be (176 ± 11) mg.</td>
<td></td>
</tr>
<tr>
<td><strong>Copper Wire Winding</strong></td>
<td>Same as component requirements</td>
<td>Not specified</td>
<td>The wire shall be wound so that it is in contact with the frame and is uniform. The proximal and distal ends of the wire must lie smoothly on the T surface and not protrude beyond the wire profile in order to prevent any chance abrasion of uterine tissue during insertion or in situ. The length of wire protruding from the anchoring hole (“the tag”) shall not exceed 10 mm. It shall be bent down to run parallel to the vertical stem and not interfere with the position of the arms when the IUD is placed in the insertion device. Both single- and double-wound configurations are acceptable. The wire shall be wound so that it is in contact with the frame and is uniform. The proximal and distal ends of the wire must lie smoothly on the T surface and not protrude beyond the wire profile in order to prevent any chance abrasion of uterine tissue during insertion or in situ. The length of wire protruding from the anchoring hole (“the tag”) shall not exceed 10 mm. It shall be bent to point down the vertical stem and not interfere with the position of the arms when the IUD is placed in the insertion device. Both single- and double-wound configurations are acceptable.</td>
<td></td>
</tr>
</tbody>
</table>
# Summary of Specification Changes

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Insertion Tube</td>
<td>Same as component requirements</td>
<td>Same as component requirements</td>
<td>Same as component requirements</td>
<td>The length of the insertion tube shall be (206 ± 2) mm.</td>
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<tr>
<td></td>
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<td></td>
<td>The internal diameter of the insertion tube shall be not less than (3.7 + 0.2/- 0.1) mm. This should be determined using a plug gauge.</td>
</tr>
<tr>
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<td></td>
<td>The outside diameter of the insertion tube shall be (4.4 + 0.2/- 0.1) mm.</td>
</tr>
<tr>
<td>Insertion rod</td>
<td>Same as component requirements</td>
<td>Not specified</td>
<td>Same as component requirements</td>
<td>The length of the insertion rod shall be (190 ± 5) mm from handle brace to tip.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The insertion rod shall be a snug fit but slide smoothly within the insertion tube and shall not trap the thread.</td>
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<td></td>
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<td></td>
<td></td>
<td>It is recommended that the rod have a thickened section, spline or ridge, to help retain the rod within the insertion tube.</td>
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<td></td>
<td>The diameter of the insertion rod at tip shall be (2.6 ± 0.2) mm. The rod diameter should be equal to or less than the tip diameter.</td>
</tr>
<tr>
<td>Insertion Tube Flange</td>
<td>Same as component requirements</td>
<td>Not specified</td>
<td>Same as component requirements</td>
<td>The shape and dimensions of the central hole shall be such that the specified flange displacement force specification is met.</td>
</tr>
<tr>
<td>Breaking strength</td>
<td>0.907 kg (8.89 N)</td>
<td>9.5 N for T-shaped frame devices</td>
<td>When tested according to ISO 7439:2002, Clause 7 the peak load at break shall be greater than 9.5 Newton.</td>
<td>The breaking force of the finished product after sterilization shall be greater than 9.5 Newton.</td>
</tr>
<tr>
<td>Copper collar retention force</td>
<td>Not specified</td>
<td>Not Specified</td>
<td>The minimum force required to displace a collar on the arm shall be 6.86 Newton (700 g-force).</td>
<td>The minimum force required to displace a collar on the arm shall be 6.86 Newton (700 g-force) when tested using a separation speed of (200 ± 20) mm/min.</td>
</tr>
<tr>
<td>Memory</td>
<td>Maximum 5 mm after one minute’s recovery from the 5-minute folded state</td>
<td>Deformation not more than 5 mm after one minute’s recovery</td>
<td>Maximum 5 mm after one minute’s recovery from the 5-minute folded state.</td>
<td>When the finished product after sterilization is tested according to relevant clause of ISO 7439, the maximum displacement from horizontal of the horizontal arms shall be not greater than 5.0 mm.</td>
</tr>
</tbody>
</table>

TCu380A Intrauterine Contraceptive Device (IUD)  
89
### Summary of Specification Changes

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Thread knot</td>
<td>Not specified</td>
<td>Not Specified</td>
<td>The knot shall be secure and not promote breakage under normal use.</td>
<td>The knot shall be secure. An insecure thread knot is considered a defect (see Clause 4.7 product defects).</td>
</tr>
<tr>
<td>Insertion rod</td>
<td>Same as component requirements</td>
<td>Not Specified</td>
<td>The insertion rod shall be a snug fit but slide smoothly within the insertion tube and shall not trap the thread.</td>
<td>The insertion rod shall be a snug fit but slide smoothly within the insertion tube and shall not trap the thread.</td>
</tr>
<tr>
<td>Flange displacement force</td>
<td>(0.209 to 0.907) kg</td>
<td>Not Specified</td>
<td>The required force to achieve a steady displacement of the flange should be between 2.0 and 9.0 Newton.</td>
<td>The required force to achieve a steady displacement of the flange shall be between 2.0 and 9.0 Newton.</td>
</tr>
<tr>
<td>Product Defects</td>
<td>Not specified</td>
<td>Assessed by visual examination, not measurement. Defects divided into critical and non-critical. Lists of critical and non-critical defects included.</td>
<td>Finished IUDs should be inspected visually for evidence of visible defects. The severity of defects may vary depending upon the level of impact they may have on the safety, effectiveness and acceptability of the product. The number of pieces to be inspected are given in Section 3.7. All IUDs comprising the sample shall comply with the requirements for visible defects. No distinction between critical and non-critical defects. List of defects included.</td>
<td></td>
</tr>
</tbody>
</table>
Annex III

IUD Technical Drawings

TCu380A Intrauterine Contraceptive Device (IUD)
The thread shall be formed to form two coils, approximately equal length.
The length of each coil shall be not less than 105 mm and not greater than 125 mm.

The thread diameter shall be 0.25 ± 0.05 mm.
1 Letter of Application

All product dossiers and site master files submitted must be accompanied by a cover letter expressing interest in participating in the UNFPA prequalification process and confirming that the information submitted in the Product Dossier and Site Master File summary is complete and correct. Below is an example of such a letter.

Date _________________________________

To: United Nations Population Fund
   Procurement Services Branch
   Marmorvej 51
   DK 2100 Copenhagen 0
   Denmark

Sir/Madam:

Being duly authorized to represent and act on behalf of [name of manufacturer] (hereinafter referred to as the "Applicant") and having reviewed and fully understood all the information on prequalification provided, the undersigned hereby applies to be prequalified by UNFPA as potential supplier of TCu380A intrauterine devices.

Attached to this letter are copies of original documents defining:
- the Applicant’s legal status;
- product dossier;
- site master file summary;
- sample products.

UNFPA and its authorized representatives are hereby authorized to conduct any enquiries or investigations to verify the statements, documents and information submitted in connection with this application and to seek clarification from our bankers and clients regarding any financial and technical aspects.

This Letter of Application will also serve as authorization to any individual or authorized representative of any institution referred to in the supporting documentation to provide such information deemed necessary and requested by yourselves to verify statements and information provided in this application or with regard to the resources, experience and competence of the Applicant.

The Applicant declares that all the information provided with the application is valid.

Name of Applicant [Manufacturer] __________________________________________
Name of Responsible Officer __________________________________________
Signature __________________________________________
Position/Title __________________________________________
Date __________________________________________
2  TCu380A IUD Product Dossier Requirements

2.1  Brand names
Provide a list of approved brand names.

2.2  Samples
Provide 10 (ten) samples of each IUD in its final packaging to enable visual inspection of the product, the packaging materials and the label.

2.3  Local, country and regional regulatory approval for the product
List the countries in which:
• the product has been registered and granted a marketing authorization
• an application for marketing authorization is currently pending
• the product has been withdrawn from the market
• any marketing approval has been revoked within the past five years.

2.4  Raw materials
List all raw materials, including copper and packaging. Complete the following table. Add additional explanatory information if required and modify the table as necessary (e.g. lubricants, cleaning materials for the primary components including function chemical name and manufacturer.)

<table>
<thead>
<tr>
<th>Component</th>
<th>Material/Quantity</th>
<th>Manufacturer &amp; Manufacturer Address</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-frame</td>
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<td></td>
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<tr>
<td>Plastic</td>
<td></td>
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<tr>
<td>Filler</td>
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<tr>
<td>Quantity of filler (%)</td>
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<tr>
<td>Thread</td>
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<tr>
<td>Plastic</td>
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<tr>
<td>Filler</td>
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<td></td>
<td></td>
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<tr>
<td>Quantity of filler (%)</td>
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<tr>
<td>Insertion tube</td>
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<td></td>
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<tr>
<td>Plastic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filler (if applicable)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Insertion rod</td>
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<td></td>
<td></td>
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<tr>
<td>Plastic</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Filler/Pigment (if applicable)</td>
<td></td>
<td></td>
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<tr>
<td>Positioning flange</td>
<td></td>
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<tr>
<td>Plastic</td>
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<td></td>
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<tr>
<td>Filler/Pigment (if applicable)</td>
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<tr>
<td>Individual pouch</td>
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<tr>
<td>Material</td>
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<td></td>
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<tr>
<td>Upper film</td>
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<td></td>
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<tr>
<td>Lower film</td>
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<td></td>
<td></td>
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<tr>
<td>Copper components</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Copper wire</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper Collar</td>
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</tr>
</tbody>
</table>
2.5 Evidence of biocompatibility

The following information is required:

• Verification that biocompatibility testing has been carried out in accordance with the WHO/UNFPA TCu380A IUD Technical Specification. This should include summary reports of testing including toxicologists’ expert reports.

2.6 Stability

The following information is required:

• Stability reports demonstrating product remains in conformance with Specification up to the claimed latest insertion date.

2.7 Processes for bioburden control and terminal sterilization

• Describe the procedures used to control and monitor the bioburden on the product, and method terminal sterilization. Procedures shall align with the WHO/UNFPA TCu380A IUD Technical Specification given in Chapter 4.

• Provide details of validation procedures for bioburden measurement.

• Provide full details including name and address of contract facilities used for the sterilization process.

• Provide validation certificates and/or reports for the sterilization process.

• Provide copies of sterilization facility certificates. ISO 13485 is required. In the absence of ISO 13485, ISO 9001 or other appropriate certification may be accepted.

• Provide data on residual ethylene oxide and ethylene chlorohydrin levels if appropriate.

2.8 Product dimensional specifications

Indicate any deviations from the WHO/UNFPA TCu380A IUD Technical Specification if appropriate.

2.9 In-process control and product release testing

• Provide a description of the tests and acceptance criteria performed at the critical steps in the manufacturing process, the critical process controls, and achieved capability (a sampling plan showing where, when and how the samples are taken should be provided). Describe any deviations from the test methods given in the WHO/UNFPA TCu380A IUD Technical Specification.

• Provide final release test reports on three Lots and demonstrate conformance with WHO/UNFPA TCu380A IUD Technical Specification requirements.

2.10 Packaging and labelling specifications:

• Provide the product specification for the primary package insert, inner box, and the exterior shipping carton. This may include artwork and photographs.

• Provide examples of labelling. If labelling does not comply with the WHO/UNFPA TCu380A IUD Technical Specification, explain how this can be changed.

2.11 Risk management of the product

Provide a Risk Management Plan for the product according to the latest edition of ISO 14971.

2.12 Design and development

A brief description of procedures used to control design and development.

3 Site Master File Requirements

3.1 General information

• Name and exact address of the site, including telephone, fax, e-mail, and 24-hour contact telephone numbers.

• Brief information about the corporate structure, including the holding or parent company, affiliates, subsidiaries and partners.

• Total manufacturing capacity of the site, including:
  - moulding
  - assembly
  - packaging
  - sterilization.

• Length of time that TCu380A IUDs have been manufactured at this manufacturing site. Length of time manufacturing TCu380A IUDs at other sites.

• What other, if any, types of products are manufactured or manufacturing activities take place at this site.

• Actual sales in past three years for the manufacturing site.

3.2 Manufacturing certifications

List and provide copies of all relevant certifications, including ISO 13485. Also supply ISO 9000 and ISO 14001 series, if applicable.

Provide a copy of the last ISO 13485 audit report.
3.3 Personnel

- List the total number of persons employed in the respective TCu380A IUD manufacturing site(s).
- List the numbers employed, by category: senior management, production management, quality assurance, quality control, maintenance and administration.
- An organization chart showing all management and supervisory positions, including arrangements for quality assurance and quality control.
- A brief summary of the qualifications, experience and responsibilities of key personnel, senior managers and directors, quality assurance supervisors, production manager/director and laboratory manager/director, if appropriate.
- A summary of policy and procedure for meeting health requirements of personnel engaged in production.
- A brief description of the staff training scheme, the structure and maintenance of training records, and the policy and method for ensuring verifiable competence.
- A brief summary of personnel hygiene and safety requirements, including protective clothing.
- Confirmation that there is a written health and safety policy, and a summary of the key components of this policy.
- Information on the use of any outside scientific, analytical or other technical assistance in relation to manufacture and analysis.
- Operating hours and shifts for personnel. Indicate out-of-office hours arrangements, responsibilities and authority.

3.4 Premises and equipment

- A simple plan or description of the manufacturing areas with an indication of scale (architectural or engineering drawings not required).
- A description of the systems and procedures used to control the bioburden on the product prior to terminal sterilization including brief descriptions of:
  - the nature of the construction and finishes of floors, ceilings, and walls;
  - ventilation systems, including steps taken to prevent product contamination;
  - procedures for cleaning manufacturing areas and equipment;
  - procedures for the control of staff entering designated clean areas including dress code and hand washing/cleanliness requirements;
  - procedures for laundering clothing;
  - procedures for monitoring bioburden levels in the production areas and on the product; and
  - copies of bioburden validation reports.
- A concise description of planned maintenance programmes for the premises.
- A brief description of the main equipment used in production and control laboratories, including major computer systems used for production and quality control (a full list of equipment is not required);
- A brief description of the preventative maintenance programmes for production equipment, equipment used in the production and control laboratories and any recording system.
- A brief description of validation protocols and calibration procedures, including arrangements for validating computerized systems and accreditations, for external laboratories providing traceable calibrations.

3.5 Records

Describe briefly arrangements for the safe storage and retrieval of records.

3.6 Production

Provide the following related to production processes.

- A brief description of production operations, using, whenever possible, flow sheets and charts and specify important parameters. Include a brief description of the scale of production, identify equipment by type (e.g. testing machines) and state working capacity, where relevant.
- A summary of the procedures for handling starting materials, work in progress, packaging materials and finished products, including sampling, quarantine, release and storage.
- A brief description of arrangements for handling rejected materials and products.
- A brief description of the general policy for process validation and a summary of the master validation plan processes and the whole facility.

3.7 Quality Management System

Quality control

Provide an overview of the quality control system including procedures designed to control the quality of incoming raw materials, work in progress and finished product. Include tests conducted at the critical stages of the manufacturing process including an indication of samples sizes used.

Quality control procedures should reflect those required for a sterile implantable product and should include bioburden control and freedom from contamination.
**Annex IV  Product Dossier and Site Master File Requirements for Prequalification**

**Documentation control**
Describe briefly arrangements for preparing, revising and distributing all necessary management system documentation.

**Risk management plan**
A summary of the risk management assessment for the manufacturing process undertaken in accordance with ISO 14971 and the resulting risk management plan.

**Self-inspection (internal audits)**
- A brief description of the self-inspection (internal audit) system.
- A copy of the last internal audit report.

**Corrective and preventative action**
A brief description of procedures and arrangements for identifying, implementing and completing corrective and preventative actions.

**Distribution, complaints and product recall**
- A brief description of the arrangements and recording system for distribution.
- A brief description of the arrangements for handling post-production monitoring and vigilance reporting, complaints and product recalls.
## Annex V

### Guide for Prequalification Inspection

### 1 Inspection Guide

<table>
<thead>
<tr>
<th>Area under inspection</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>1 General company details</strong></td>
<td></td>
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<tr>
<td>Address and contact details</td>
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<tr>
<td>IUD designs manufactured</td>
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<tr>
<td>Independent certification of systems and products, including regulatory approvals</td>
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<tr>
<td>Markets supplied</td>
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<tr>
<td>Operating hours and shifts</td>
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<tr>
<td><strong>2 Human resources</strong></td>
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<tr>
<td>Management team and key staff, including authority and responsibilities</td>
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<tr>
<td>Organization chart reflects operations</td>
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<tr>
<td>Out-of-office hours arrangements, responsibilities and authority</td>
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<tr>
<td>Staff selection, induction and training systems.</td>
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<td>Staff training records are up to date and valid</td>
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<tr>
<td><strong>3 Production capacity throughout the operation</strong></td>
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<tr>
<td>Number and type of machines</td>
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<tr>
<td>Quoted output and yields</td>
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<td>Product realization and planning</td>
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<tr>
<td><strong>4 Raw materials</strong></td>
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<tr>
<td>Purchasing</td>
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<td>Selection, storage and quality</td>
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<td>Supplier evaluation and validation</td>
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<td>Acceptance and storage procedures</td>
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<tr>
<td>Status indication, labelling and documentation</td>
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<tr>
<td>Environment</td>
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<tr>
<td><strong>5 Preparation of compounded materials</strong></td>
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<tr>
<td>Where undertaken</td>
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<tr>
<td>Process</td>
<td></td>
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<tr>
<td>Testing and controls</td>
<td></td>
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<tr>
<td>Documentation and labelling</td>
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<tr>
<td>Environment</td>
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<tr>
<td><strong>6 Moulding</strong></td>
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<tr>
<td>Materials used</td>
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<td>Sourcing</td>
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<tr>
<td>Process and equipment validation</td>
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<tr>
<td>Process controls and monitoring</td>
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<tr>
<td>Annex V</td>
<td>Guide for Prequalification Inspection</td>
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<tr>
<td>Environmental and personnel hygiene controls</td>
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<tr>
<td>Production quality control</td>
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<tr>
<td>Production bioburden validation</td>
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<tr>
<td>Identification, traceability and status</td>
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<tr>
<td>Storage and disposition of non-conforming and rejected goods</td>
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<tr>
<td><strong>7 Assembly</strong></td>
<td></td>
</tr>
<tr>
<td>Equipment</td>
<td></td>
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<tr>
<td>Process</td>
<td></td>
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<tr>
<td>Process and equipment validation</td>
<td></td>
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<tr>
<td>Process controls and monitoring</td>
<td></td>
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<tr>
<td>Environmental and personnel hygiene controls</td>
<td></td>
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<tr>
<td>Product quality control</td>
<td></td>
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<tr>
<td>Product bioburden validation</td>
<td></td>
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<tr>
<td>Storage and disposition of non-conforming and rejected goods</td>
<td></td>
</tr>
<tr>
<td><strong>8 Provisions for storage and control of components, work in progress, and finished products</strong></td>
<td></td>
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<tr>
<td>Segregation</td>
<td></td>
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<tr>
<td>Labelling</td>
<td></td>
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<tr>
<td>Status identification</td>
<td></td>
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<tr>
<td>Environment</td>
<td></td>
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<tr>
<td>Security</td>
<td></td>
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<tr>
<td><strong>9 Packaging</strong></td>
<td></td>
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<tr>
<td>Materials used</td>
<td></td>
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<tr>
<td>Process</td>
<td></td>
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<tr>
<td>Adequacy of equipment</td>
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<tr>
<td>Testing and controls</td>
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<tr>
<td>Documentation and labelling</td>
<td></td>
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<tr>
<td>Definition and understanding of Lot coding</td>
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<tr>
<td>Equipment and process validation protocols and reports</td>
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<tr>
<td>Environment</td>
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<tr>
<td><strong>10 Sterilization</strong></td>
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<tr>
<td>Where undertaken</td>
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<tr>
<td>Methods used</td>
<td></td>
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<tr>
<td>Testing and controls including bioburden validation and monitoring</td>
<td></td>
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<tr>
<td>Product sterility validation</td>
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<tr>
<td>Sterilizer validation</td>
<td></td>
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<tr>
<td>Documentation and labelling</td>
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<tr>
<td>Verify sterilizer certification</td>
<td></td>
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</tbody>
</table>

| Area under inspection | Comments |
### 11 Warehousing
- Adequacy
- Segregation
- Labelling
- Stock control and rotation
- Presence of aged or non-conforming goods

### 12 Distribution procedures
- Agreements
- Confirm adequate recording of product distribution

### 13 Quality control plan
- Details of product testing at each stage of manufacturing process, including Lot release

### 14 Outgoing product quality
- Verification of conformance of product and process capability

### 15 Quality system and documentation
- Quality policy and objectives
- Quality manual
- Standard operating procedures (SOPs) and work instructions (WIs)
- Documented versus actual practices
- Document control
- Process approach
- Contract review
- Risk management
- Validation policy and management
- Complaints, recall, vigilance and advisory notices
- Post-market surveillance
- Audit
- Control of non-conforming product (corrective and preventive action)
- LOT traceability
- Statistical analysis of collected data
- Product master file
- Management review
- Improvement

### 16 Maintenance
- Documented programme, including schedule
- Details of maintenance for key areas and records
- Adequacy of programme monitoring and effectiveness assessment

<table>
<thead>
<tr>
<th>Area under inspection</th>
<th>Comments</th>
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<tbody>
<tr>
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</tbody>
</table>
### 17 Laboratory facilities, competence and calibration

Routine activities of each laboratory  
Equipment and methods  
Reporting of results and documentation  
Calibration system  
Certifications  
Participation in inter-laboratory trials  
Research and development  
Understanding and competence

### 18 Shelf-life and stability

Verification that the facilities and procedures used for shelf life verification are acceptable.

Details of Studies  
Retention sample programme

### 19 Buildings, grounds and services

Buildings and premises  
Clean-room particulate count  
Overall fabrication and condition of premises  
Pest and rodent control  
Air handling  
Compressed air  
Electricity

### Reference

- [http://whqlibdoc.who.int/trs/WHO_TRS_948_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_948_eng.pdf?ua=1)  
### Glossary of Terms and Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABS</td>
<td>Acrylonitrile-butadiene-styrene polymer</td>
</tr>
<tr>
<td>Acceptance Number</td>
<td>The highest number of non-compliers (failures) allowed in a specific test from a selected sample</td>
</tr>
<tr>
<td>ANSI/AAMI</td>
<td>American National Standards Institute/American Association for Medical InstrumentsAQL Acceptable Quality Limit. The quality level that is the worst tolerable process average when a continuing series of Lots is submitted for acceptance sampling (ISO 2859-1). Note: Manufacturers should be consistently achieving a process average that is better than the AQL</td>
</tr>
<tr>
<td>ASTM</td>
<td>American Society for Testing Materials</td>
</tr>
<tr>
<td>AWG</td>
<td>American Wire Gauge</td>
</tr>
<tr>
<td>Batch</td>
<td>A term sometimes used in place of “Lot” (see definition of Lot). WHO recommends “Lot” be used when referring to medical devices. “Batch” also can refer to a quantity of individual raw materials</td>
</tr>
<tr>
<td>Bioburden</td>
<td>The population of microorganisms on a raw material, a component, product, packaging or equipment</td>
</tr>
<tr>
<td>CE mark</td>
<td>On medical product packaging, a mark certifying that the product conforms to the essential requirements of the European medical device directive 93/42/EEC</td>
</tr>
<tr>
<td>CPM</td>
<td>Critical Performance Measurement</td>
</tr>
<tr>
<td>CPPM</td>
<td>Critical Product Package Measurement</td>
</tr>
<tr>
<td>Critical defects</td>
<td>Defects that might affect the safety, acceptability and/or effectiveness of the product are classified as critical defects, causing the device to be rejected</td>
</tr>
<tr>
<td>EOI</td>
<td>Expression of Interest</td>
</tr>
<tr>
<td>Expiry date</td>
<td>The date after which raw materials, components, etc. are no longer considered acceptable for manufacturing IUDs</td>
</tr>
<tr>
<td>FEFO</td>
<td>First expiry, first out basis</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice. A code of practice aimed at ensuring that product is consistently manufactured to the required standard</td>
</tr>
<tr>
<td>FHI</td>
<td>Family Health International. The organization now goes by the name FHI 360</td>
</tr>
<tr>
<td>HDPE</td>
<td>High-Density Polyethylene</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>Inspection level</td>
<td>The degree of examination of the Lot, as specified in ISO 2859-1. The higher the inspection level, the more samples that will be tested, and hence the lower the risk of faulty products reaching the consumer</td>
</tr>
<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
</tr>
<tr>
<td>ISWG</td>
<td>Imperial Standard Wire Gauge</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine Device</td>
</tr>
<tr>
<td>Latest Insertion Date (LID)</td>
<td>The date after which the device should not be inserted into the uterus. (Occasionally, the term “expiry date” is used, but this can be confused with the latest date at which the device has to be removed from the uterus. The use of “expiry date” is therefore discouraged.)</td>
</tr>
<tr>
<td>LDPE</td>
<td>Low-Density Polyethylene</td>
</tr>
</tbody>
</table>
### Glossary Terms and Abbreviations

| **LOT** | A Lot is a homogeneous collection of IUDs made under essentially identical manufacturing conditions using the same Lots of raw materials: low-density polyethylene (LDPE) compound, high-density polyethylene (HDPE) compound, for thread, copper for wire and collars, individual pouches and individual pouch material that are subjected to sterilization in the same sterilization cycle and assigned a unique number before release. Clear Lot identification and recording are required to permit effective product recall in the event of a quality problem with the device.
|
| **LOT number or code** | A unique identifying alphanumeric code assigned to a Lot.
|
| **MSI** | Marie Stopes International.
|
| **Non-critical defects** | Defects that might affect the acceptability of the product, causing the device to be rejected at the time of insertion, but are not expected to affect safety or effectiveness of the device.
|
| **NDA** | New Drug Application.
|
| **OFE** | Oxygen-Free Electronic.
|
| **OFHC** | Oxygen-Free High Conductivity.
|
| **Package** | The film-film or film-Tyvek peel pouch in which the IUD is sealed after manufacture and sterilization.
|
| **PD** | Product Dossier.
|
| **Ph. Eur.** | European Pharmacopoeia.
|
| **PI** | Pearl Index.
|
| **PP** | Polypropylene.
|
| **Prequalification** | The steps taken by the buyer to verify a manufacturer’s suitability to provide IUDs of the required quality. The WHO/UNFPA Prequalification Programme includes periodic assessment of manufacturing dossiers, testing of samples and manufacturer inspection.
|
| **Process average** | The percentage of non-conforming IUDs over a defined time period or quantity of production. It is calculated for each requirement detailed in the *WHO/UNFPA TCu380A IUD Technical Specification* by dividing the number of non-conforming IUDs by the total number of IUDs tested. Ideally, the process average for a specific attribute should not be greater than half the specified AQL.
|
| **Random sample** | A sample of IUDs drawn randomly from a LOT for testing purposes.
|
| **RH** | Relative Humidity.
|
| **SAL** | Sterility Assurance Level.
|
| **Sampling plan** | A specific plan that indicates the number of units (IUDs) from each LOT that are to be inspected (sample size) and the associated criteria for determining the acceptability of the LOT (acceptance and rejection numbers).
|
| **Shelf life** | The period of time after manufacture that the product is considered suitable for insertion, stated as the Latest Insertion Date on the pack.
|
| **SMF** | Site Master File summary.
|
| **SOP** | Standard Operating Procedure.
|
| **Specification** | A detailed statement of a product’s requirements as established by the buyer. Usually, a specification is based on an established standard.
|
| **Standard** | A detailed statement of the minimum acceptance requirements, as established by a national or international regulatory body.
### Glossary  Terms and Abbreviations

<table>
<thead>
<tr>
<th>UNFPA</th>
<th>United Nations Population Fund</th>
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<tbody>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
</tr>
<tr>
<td>U.S. FDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>USP</td>
<td>United States Pharmacopeia</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WHO/RHR</td>
<td>World Health Organization, Department of Reproductive Health and Research</td>
</tr>
</tbody>
</table>
This document has been prepared in consultation with representatives from:

Crown Agents
Department for International Development (DFID)
International Planned Parenthood Federation (IPPF)
International Standardization Organization (ISO) Technical Committee 157
John Snow, Inc. (JSI)
Population Services International (PSI)
Population Action International (PAI)
Program for Appropriate Technology in Health (PATH)
Reproductive Health Supplies Coalition (RHSC)
U.S. Agency for International Development (USAID)
U.S. Centers for Disease Control and Prevention (CDC)
World Bank